

Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage<https://doi.org/10.1038/s41467-019-08853-3> "Antimicrobial resistance (AMR) is a serious threat to global public health, but obtaining representative data on AMR for healthy human populations is difficult. Here, we use metagenomic analysis of untreated sewage to characterize the bacterial resistome from 79 sites in 60 countries. We find systematic differences in abundance and diversity of AMR genes between Europe/North-America/Oceania and Africa/Asia/South-America. Antimicrobial use data and bacterial taxonomy only explains a minor part of the AMR variation that we observe. We find no evidence for cross-selection between antimicrobial classes, or for effect of air travel between sites. However, AMR gene abundance strongly correlates with socio-economic, health and environmental factors, which we use to predict AMR gene abundances in all countries in the world. Our findings suggest that global AMR gene diversity and abundance vary by region, and that improving sanitation and health could potentially limit the global burden of AMR. We propose metagenomic analysis of sewage as an ethically acceptable and economically feasible approach for continuous global surveillance and prediction of AMR."

"Antimicrobial resistance in humans, livestock and the wider environment"

<https://doi.org/10.1098/rstb.2014.0083> "Antimicrobial resistance (AMR) in humans is inter-linked with AMR in other populations, especially farm animals, and in the wider environment. The relatively few bacterial species that cause disease in humans, and are the targets of antibiotic treatment, constitute a tiny subset of the overall diversity of bacteria that includes the gut microbiota and vast numbers in the soil. However, resistance can pass between these different populations; and homologous resistance genes have been found in pathogens, normal flora and soil bacteria. Farm animals are an important component of this complex system: they are exposed to enormous quantities of antibiotics (despite attempts at reduction) and act as another reservoir of resistance genes. Whole genome sequencing is revealing and beginning to quantify the two-way traffic of AMR bacteria between the farm and the clinic. Surveillance of bacterial disease, drug usage and resistance in livestock is still relatively poor, though improving, but achieving better antimicrobial stewardship on the farm is challenging: antibiotics are an integral part of industrial agriculture and there are very few alternatives. Human production and use of antibiotics either on the farm or in the clinic is but a recent addition to the natural and ancient process of antibiotic production and resistance evolution that occurs on a global scale in the soil. Viewed in this way, AMR is somewhat analogous to climate change, and that suggests that an intergovernmental panel, akin to the Intergovernmental Panel on Climate Change, could be an appropriate vehicle to actively address the problem."

Achieving global targets for antimicrobial resistance

<https://doi.org/10.1126/science.aaf9286> "The UN should promote targets, funding, and governance"

Sources of Antimicrobial Resistance <https://doi.org/10.1126/science.1243444>

Genomic data help to elucidate the role of food animals in the spread of antimicrobial resistance in humans. [Also see Report by Mather et al.]

Using sewage for surveillance of antimicrobial resistance

<https://doi.org/10.1126/science.aba3432> A global system would exploit metagenomic sequencing

Policy: An intergovernmental panel on antimicrobial resistance

<https://doi.org/10.1038/509555a>

Global governance of antimicrobial resistance [https://doi.org/10.1016/s0140-6736\(18\)31117-6](https://doi.org/10.1016/s0140-6736(18)31117-6)

The role of ‘filth flies’ in the spread of antimicrobial resistance

<https://doi.org/10.1016/j.tmaid.2018.02.007> "‘Filth flies’ feed and develop in excrement and decaying matter and can transmit enteric pathogens to humans and animals, leading to colonization and infection. Considering these characteristics, ‘filth flies’ are potential vectors for the spread of antimicrobial resistance (AMR). This review defines the role of flies in the spread of AMR and identifies knowledge gaps. The literature search (original articles, reviews indexed for PubMed) was restricted to the English language. References of identified studies were screened for additional sources. ‘Filth flies’ are colonized with antimicrobial-resistant bacteria of clinical relevance. This includes extended spectrum beta-lactamase-, carbapenemase-producing and colistin-resistant (mcr-1 positive) bacteria. Resistant bacteria in flies often share the same genotypes with bacteria from humans and animals when their habitat overlap. The risk of transmission is most likely highest for enteric bacteria as they are shed in high concentration in excrements and are easily picked up by flies. ‘Filth flies’ can ‘bio-enhance’ the transmission of AMR as bacteria multiply in the digestive tract, mouthparts and regurgitation spots. To better understand the medical importance of AMR in flies, quantitative risk assessment models should be refined and fed with additional data (e.g. vectorial capacity, colonization dose). This requires targeted ecological, epidemiological and in vivo experimental studies."

The rumen microbiome as a reservoir of antimicrobial resistance and pathogenicity genes is directly affected by diet in beef cattle <https://doi.org/10.1186/s40168-017-0378-z>

"The emergence and spread of antimicrobial resistance is the most urgent current threat to human and animal health. An improved understanding of the abundance of antimicrobial resistance genes and genes associated with microbial colonisation and pathogenicity in the animal gut will have a major role in reducing the contribution of animal production to this problem. Here, the influence of diet on the ruminal resistome and abundance of pathogenicity genes was assessed in ruminal digesta samples taken from 50 antibiotic-free beef cattle, comprising four cattle breeds

receiving two diets containing different proportions of concentrate. Two hundred and four genes associated with antimicrobial resistance (AMR), colonisation, communication or pathogenicity functions were identified from 4966 metagenomic genes using KEGG identification. Both the diversity and abundance of these genes were higher in concentrate-fed animals. Chloramphenicol and microcin resistance genes were dominant in samples from forage-fed animals ($P < 0.001$), while aminoglycoside and streptomycin resistances were enriched in concentrate-fed animals. The concentrate-based diet also increased the relative abundance of Proteobacteria, which includes many animal and zoonotic pathogens. A high ratio of Proteobacteria to (Firmicutes + Bacteroidetes) was confirmed as a good indicator for rumen dysbiosis, with eight cases all from concentrate-fed animals. Finally, network analysis demonstrated that the resistance/pathogenicity genes are potentially useful as biomarkers for health risk assessment of the ruminal microbiome. Diet has important effects on the complement of AMR genes in the rumen microbial community, with potential implications for human and animal health."

PERSPECTIVE: Evolutionary biology and the avoidance of antimicrobial resistance

<https://doi.org/10.1111/j.1752-4571.2008.00066.x> "Evolutionary biologists have largely left the search for solutions to the drug resistance crisis to biomedical scientists, physicians, veterinarians and public health specialists. We believe this is because the vast majority of professional evolutionary biologists consider the evolutionary science of drug resistance to be conceptually uninteresting. Using malaria as case study, we argue that it is not. We review examples of evolutionary thinking that challenge various fallacies dominating antimalarial therapy, and discuss open problems that need evolutionary insight. These problems are unlikely to be resolved by biomedical scientists ungrounded in evolutionary biology. Involvement by evolutionary biologists in the science of drug resistance requires no intellectual compromises: the problems are as conceptually challenging as they are important."

Genomic analysis of sewage from 101 countries reveals global landscape of antimicrobial resistance <https://doi.org/10.1038/s41467-022-34312-7> "Abstract Antimicrobial resistance (AMR) is a major threat to global health. Understanding the emergence, evolution, and transmission of individual antibiotic resistance genes (ARGs) is essential to develop sustainable strategies combatting this threat. Here, we use metagenomic sequencing to analyse ARGs in 757 sewage samples from 243 cities in 101 countries, collected from 2016 to 2019. We find regional patterns in resistomes, and these differ between subsets corresponding to drug classes and are partly driven by taxonomic variation. The genetic environments of 49 common ARGs are highly diverse, with most common ARGs carried by multiple distinct genomic contexts globally and sometimes on plasmids. Analysis of flanking sequence revealed ARG-specific patterns of dispersal limitation and global transmission. Our data furthermore suggest certain

geographies are more prone to transmission events and should receive additional attention."

3D bioprinting of mature bacterial biofilms for antimicrobial resistance drug testing

<https://doi.org/10.1088/1758-5090/ab37a0>

"The potential to bioprint and

study 3D bacterial biofilm constructs could have great clinical significance at a time when antimicrobial resistance is rising to dangerously high levels worldwide. In this study, clinically relevant bacterial species including *Escherichia coli*, *Staphylococcus aureus* (MSSA), Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* were 3D bioprinted using a double-crosslinked alginate bioink to form mature bacteria biofilms, characterized by confocal laser scanning microscopy (CLSM) and fluorescent staining. Solid and porous bacteria-laden constructs were reproducibly bioprinted with thicknesses ranging from 0.25 to 4 mm. We demonstrated 3D bioprinting of thicker biofilms (>4 mm) than found in currently available in vitro models. Bacterial viability was excellent in the bioprinted constructs, with CLSM observation of bacterial biofilm production and maturation possible for at least 28 d in culture. Importantly, we observed the complete five-step biofilm life cycle in vitro following 3D bioprinting for the first time, suggesting the formation of mature 3D bioprinted biofilms. Bacterial growth was faster in thinner, more porous constructs whilst constructs crosslinked with BaCl₂ concentrations of above 10 mM had denser biofilm formation. 3D MRSA and MSSA biofilm constructs were found to show greater resistance to antimicrobials than corresponding two-dimensional (2D) cultures. Thicker 3D *E. coli* biofilms had greater resistance to tetracycline than thinner constructs over 7 d of treatment. Our methodology allowed for the precise 3D bioprinting of self-supporting 3D bacterial biofilm structures that developed biofilms during extended culture. 3D biofilm constructs containing bacterial biofilms produce a model with much greater clinical relevance compared to 2D culture models and we have demonstrated their use in antimicrobial testing."

Key considerations on the potential impacts of the COVID-19 pandemic on antimicrobial resistance research and surveillance

<https://doi.org/10.1093/trstmh/trab048>

"Antibiotic use in severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2) patients during the COVID-19 pandemic has exceeded the incidence of bacterial coinfections and secondary infections, suggesting inappropriate and excessive prescribing. Even in settings with established antimicrobial stewardship (AMS) programmes, there were weaknesses exposed regarding appropriate antibiotic use in the context of the pandemic. Moreover, antimicrobial resistance (AMR) surveillance and AMS have been deprioritised with diversion of health system resources to the pandemic response. This experience highlights deficiencies in AMR containment and mitigation strategies that require urgent attention from clinical and scientific communities. These include the need to implement diagnostic stewardship to assess the global incidence of coinfections and

secondary infections in COVID-19 patients, including those by multidrug-resistant pathogens, to identify patients most likely to benefit from antibiotic treatment and identify when antibiotics can be safely withheld, de-escalated or discontinued. Long-term global surveillance of clinical and societal antibiotic use and resistance trends is required to prepare for subsequent changes in AMR epidemiology, while ensuring uninterrupted supply chains and preventing drug shortages and stock outs. These interventions present implementation challenges in resource-constrained settings, making a case for implementation research on AMR. Knowledge and support for these practices will come from internationally coordinated, targeted research on AMR, supporting the preparation for future challenges from emerging AMR in the context of the current COVID-19 pandemic or future pandemics."

Clinically relevant antimicrobial resistance at the wildlife–livestock–human interface in Nairobi: an epidemiological study [https://doi.org/10.1016/s2542-5196\(19\)30083-x](https://doi.org/10.1016/s2542-5196(19)30083-x)

"BackgroundAntimicrobial resistance is one of the great challenges facing global health security in the modern era. Wildlife, particularly those that use urban environments, are an important but understudied component of epidemiology of antimicrobial resistance. We investigated antimicrobial resistance overlap between sympatric wildlife, humans, livestock, and their shared environment across the developing city of Nairobi, Kenya. We use these data to examine the role of urban wildlife in the spread of clinically relevant antimicrobial resistance. Methods99 households across Nairobi were randomly selected on the basis of socioeconomic stratification. A detailed survey was administered to household occupants, and samples (n=2102) were collected from the faeces of 75 wildlife species inhabiting household compounds (ie, the household and its perimeter; n=849), 13 livestock species (n=656), and humans (n=333), and from the external environment (n=288). *Escherichia coli*, our sentinel organism, was cultured and a single isolate from each sample tested for sensitivity to 13 antibiotics. Diversity of antimicrobial resistant phenotypes was compared between urban wildlife, humans, livestock, and the environment, to investigate whether wildlife are a net source for antimicrobial resistance in Nairobi. Generalised linear mixed models were used to determine whether the prevalence of antimicrobial resistant phenotypes and multidrug-resistant *E coli* carriage in urban wildlife is linked to variation in ecological traits, such as foraging behaviour, and to determine household-level risk factors for sharing of antimicrobial resistance between humans, wildlife, and livestock. Findings*E coli* were isolated from 485 samples collected from wildlife between Sept 6, 2015, and Sept 28, 2016. Wildlife carried a low prevalence of *E coli* isolates susceptible to all antibiotics tested (45 [9%] of 485 samples) and a high prevalence of clinically relevant multidrug resistance (252 [52%] of 485 samples), which varied between taxa and by foraging traits. Multiple isolates were resistant to one agent from at least seven antimicrobial classes tested for, and a single isolate was resistant to all antibiotics tested for in the study. The

phenotypic diversity of antimicrobial-resistant E coli in wildlife was lower than in livestock, humans, and the environment. Within household compounds, statistical models identified two interfaces for exchange of antimicrobial resistance: between both rodents, humans and their rubbish, and seed-eating birds, humans and their rubbish; and between seed-eating birds, cattle, and bovine manure. Interpretation Urban wildlife carry a high burden of clinically relevant antimicrobial-resistant E coli in Nairobi, exhibiting resistance to drugs considered crucial for human medicine by WHO. Identifiable traits of the wildlife contribute to this exposure; however, compared with humans, livestock, and the environment, low phenotypic diversity in wildlife is consistent with the hypothesis that wildlife are a net sink rather than source of clinically relevant resistance. Wildlife that interact closely with humans, livestock, and both human and livestock waste within households, are exposed to more antimicrobial resistant phenotypes, and could therefore act as conduits for the dissemination of clinically relevant antimicrobial resistance to the wider environment. These results provide novel insight into the broader epidemiology of antimicrobial resistance in complex urban environments, characteristic of lower-middle-income countries. Funding UK Medical Research Council and CGIAR Research Program on Agriculture for Nutrition and Health."

Quantifying the transmission of antimicrobial resistance at the human and livestock interface with genomics <https://doi.org/10.1016/j.cmi.2020.09.019> "Livestock have been implicated as a reservoir for antimicrobial resistance (AMR) that can spread to humans. Close proximity and ecological interfaces involving livestock have been posited as risk factors for the transmission of AMR. In spite of this, there are sparse data and limited agreement on the transmission dynamics that occur. To identify how genome sequencing approaches can be used to quantify the dynamics of AMR transmission at the human-livestock interface, and where current knowledge can be improved to better understand the impact of transmission on the spread of AMR. Key articles investigating various aspects of AMR transmission at the human-livestock interface are discussed, with a focus on Escherichia coli. We recapitulate the current understanding of the transmission of AMR between humans and livestock based on current genomic and epidemiological approaches. We discuss how the use of well-designed, high-resolution genome sequencing studies can improve our understanding of the human-livestock interface. A better understanding of the human-livestock interface will aid in the development of evidence-based and effective One Health interventions that can ultimately reduce the burden of AMR in humans."

Antimicrobial resistance research in a post-pandemic world: Insights on antimicrobial resistance research in the COVID-19 pandemic

<https://doi.org/10.1016/j.jgar.2021.02.013> "Antimicrobial resistance must be recognised as a global societal priority - even in the face of the worldwide challenge of the COVID-19 pandemic. COVID-19 has illustrated the vulnerability of our healthcare

systems in co-managing multiple infectious disease threats as resources for monitoring and detecting, and conducting research on antimicrobial resistance have been compromised during the pandemic. The increased awareness of the importance of infectious diseases, clinical microbiology and infection control and lessons learnt during the COVID-19 pandemic should be exploited to ensure that emergence of future infectious disease threats, including those related to AMR, are minimised. Harnessing the public understanding of the relevance of infectious diseases towards the long-term pandemic of AMR could have major implications for promoting good practices about the control of AMR transmission."

Assignment of virus and antimicrobial resistance genes to microbial hosts in a complex microbial community by combined long-read assembly and proximity ligation

<https://doi.org/10.1186/s13059-019-1760-x> "We describe a method that adds long-read sequencing to a mix of technologies used to assemble a highly complex cattle rumen microbial community, and provide a comparison to short read-based methods. Long-read alignments and Hi-C linkage between contigs support the identification of 188 novel virus-host associations and the determination of phage life cycle states in the rumen microbial community. The long-read assembly also identifies 94 antimicrobial resistance genes, compared to only seven alleles in the short-read assembly. We demonstrate novel techniques that work synergistically to improve characterization of biological features in a highly complex rumen microbial community."

The prevalence of antimicrobial resistance in human faecal flora in South Africa

<https://doi.org/10.1017/s0950268800056922> "Summary Between January and March 1992, 361 faecal specimens were collected from the healthy black population in the Transvaal Province of South Africa. Each specimen was examined for the prevalence of antimicrobial resistance in commensal bacteria. Volunteers, from both rural and urban dwellings, were divided into four age groups. The overall carriage rate of resistance varied from 88.6% for ampicillin, 74.2% for trimethoprim, 52.6% for chloramphenicol, 10.2% for nalidixic acid to 7.5% for gentamicin. The carriage of resistance found to each individual antimicrobial agent was slightly higher in the rural population rather than the urban population but there was no correlation between the prevalence of antimicrobial resistance and the age group."

"Measuring the global response to antimicrobial resistance, 2020–21: a systematic governance analysis of 114 countries" [https://doi.org/10.1016/s1473-](https://doi.org/10.1016/s1473-3099(22)00796-4)

[3099\(22\)00796-4](https://doi.org/10.1016/s1473-3099(22)00796-4) "Understanding strategic commitments and policy responses to overcome antimicrobial resistance at the national, regional, and global levels is required to evaluate current progress and direct future planning. National action plans (NAPs) are the primary mechanism for guiding national strategy and action for antimicrobial resistance governance. Although several NAPs have been developed, no comprehensive content analysis of these plans exists. Using a governance framework,

we aimed to assess all publicly available NAPs on antimicrobial resistance. We systematically reviewed the contents of NAPs on antimicrobial resistance from 114 countries, applying a governance framework containing 18 domains and 54 indicators in three integral areas: policy design, implementation tools, and monitoring and evaluation. As well as manually searching NAPs and doing online and literature searches that were relevant to specific indicators from repository inception to June 1, 2022, several data sources were used to generate scores, including the Tripartite Antimicrobial Resistance Country Self-Assessment Survey, the Global Antimicrobial Resistance and Use Surveillance System, the Global Antimicrobial Resistance Research and Development Hub, and various WHO datasets. NAPs were included if the country had also submitted the NAP to the Tripartite Antimicrobial Resistance Country Self-Assessment Survey 2020-21, if the NAP was retrievable through a publicly accessible database or website, and if the NAP was either published in English or eligible for machine translation. Three researchers independently reviewed each NAP and were initially blinded to the evaluations of other researchers. They generated a score using a quantification system for each of 54 indicators. The Cochrane protocol for ensuring reliability was followed. The three researchers were then unblinded and met to resolve any disagreements in scoring to reach a consensus agreement. In each case of discrepancy, consensus was reached between the researchers. We developed criteria to standardise the process of quantifying each indicator. We also weighted and collated relevant national data from various sources to generate composite scores concordant with the key governance areas. We transformed these data to a scale of 0 (worst) to 100 (best), ranked countries on the basis of their mean scores, and used descriptive statistics to analyse global and regional trends. 306 NAPs were identified and 114 were eligible for analysis. Between 2020 and 2021, the mean antimicrobial resistance governance score was 51 (SD 14). Norway had the highest governance score (mean 85 [SD 32]), and the Federated States of Micronesia had the lowest governance score (28 [37]). The highest scoring domain was participation (83 [16]), and the lowest scoring domains were accountability (30 [18]) and feedback mechanism (30 [25]). Domains relating to policy design (55 [13]) and implementation tools (54 [17]) scored similarly, whereas monitoring and evaluation (38 [20]) efforts were lower. International efforts to control antimicrobial resistance varied considerably between countries. Monitoring and evaluation efforts need improving for continuous understanding of national and international progress. International response might not be commensurate with the scale and severity of antimicrobial resistance. None."

Antimicrobial resistance and characterisation of staphylococci isolated from healthy Labrador retrievers in the United Kingdom <https://doi.org/10.1186/1746-6148-10-17>

"Coagulase-positive (CoPS) and coagulase-negative (CoNS) staphylococci are normal commensals of the skin and mucosa, but are also opportunist pathogens. Meticillin-resistant (MR) and multidrug-resistant (MDR) isolates are increasing in human

and veterinary healthcare. Healthy humans and other animals harbour a variety of staphylococci, including MR-CoPS and MR-CoNS. The main aims of the study were to characterise the population and antimicrobial resistance profiles of staphylococci from healthy non-vet visiting and non-antimicrobial treated Labrador retrievers in the UK. Nasal and perineal samples were collected from 73 Labrador retrievers; staphylococci isolated and identified using phenotypic and biochemical methods. They were also confirmed by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF-MS), PCR of the *nuc* gene and PCR and sequencing of the *tuf* gene. Disc diffusion and minimum inhibitory concentration (MIC) susceptibility tests were determined for a range of antimicrobials. In total, 102 CoPS (*S. pseudintermedius* n = 91, *S. aureus* n = 11) and 334 CoNS isolates were detected from 99% of dogs in this study. In 52% of dogs CoNS only were detected, with both CoNS and CoPS detected in 43% dogs and CoPS only detected in 4% of dogs. Antimicrobial resistance was not common among CoPS, but at least one MDR-CoNS isolate was detected in 34% of dogs. MR-CoNS were detected from 42% of dogs but no MR-CoPS were isolated. *S. epidermidis* (52% of dogs) was the most common CoNS found followed by *S. warneri* (30%) and *S. equorum* (27%), with another 15 CoNS species isolated from ≤ 15% of dogs. *S. pseudintermedius* and *S. aureus* were detected in 44% and 8% of dogs respectively. MR- and MDR-CoPS were rare. However a high prevalence of MR- and MDR-CoNS were found in these dogs, even though they had no prior antimicrobial treatment or admission to veterinary premises. These findings are of concern due to the potential for opportunistic infections, zoonotic transmission and transmission of antimicrobial resistant determinants from these bacteria to coagulase positive staphylococci."

Serotypes/groups distribution and antimicrobial resistance of invasive pneumococcal isolates: implications for vaccine strategies

<https://doi.org/10.1017/s0950268800004787> "Based on the invasive pneumococcal isolates referred to reference laboratories in Scotland in 1988-99, we identified the distribution of serotypes/groups and their antimicrobial resistance patterns in order to evaluate the coverage of polysaccharide and the new pneumococcal conjugate vaccines. A total of 5659 invasive isolates were included. Of these, 5124 (90.5%) were blood isolates, 308 (5.5%) were CSF isolates, 143 (2.5%) were blood and CSF and 84 (1.5%) were other normally sterile isolates. The most prevalent 11 serotypes/groups were 14, 9, 19, 6, 23, 1, 3, 4, 7, 8 and 18, in numerical order. These accounted for 84% of total serotypes/groups. The serotypes/groups included in the 23 and 14-valent polysaccharide vaccines accounted for 96% and 88% of all isolates. Both vaccines accounted for 98% of penicillin non-susceptible and 100% of erythromycin non-susceptible isolates. The 7, 9, and 11-valent conjugate vaccines covered 61, 68 and 80% of invasive isolates respectively. The coverage of these vaccines was substantially higher in youngest age group with 84, 86 and 93% of invasive isolates in children < 2

years included in the 7, 9 and 11-valent conjugate vaccines compared with 58, 64 and 77% in adults \geq 65 years of age. The serotype/group distribution of invasive isolates in Scotland varied from year to year over the period 1993-9. The coverage of the 23-valent vaccine remained above 95% in each year but the coverage of the 7, 9 and 11-valent conjugate vaccines showed more marked fluctuation with coverage as low as 53, 60 and 75% in some years. Continued surveillance of invasive pneumococcal isolates is required to inform the development of appropriate vaccine strategies to prevent pneumococcal disease in Scotland."

Prevalence and patterns of antimicrobial resistance among *Escherichia coli* isolated from Zambian dairy cattle across different production systems

<https://doi.org/10.1038/srep12439> "Abstract This study focused on the use of antibiotics on small, medium and commercial-sized dairy farms in the central region of Zambia and its relationship to antibiotic resistance in *Escherichia coli*. A stratified random sample of 104 farms was studied, representing approximately 20% of all dairy farms in the region. On each farm, faecal samples were collected from a random sample of animals and a standardised questionnaire on the usage of antibiotics was completed. An *E. coli* isolate was obtained from 98.67% (371/376) of the sampled animals and tested for resistance to six classes of antibiotics. The estimated prevalence of resistance across the different farming systems was: tetracycline (10.61; 95%CI: 7.40–13.82), ampicillin (6.02; 95%CI: 3.31–8.73), sulfamethoxazole/trimethoprim (4.49; 95%CI: 2.42–6.56), cefpodoxime (1.91; 95%CI: 0.46–3.36), gentamicin (0.89; 95%CI: 0.06–1.84) and ciprofloxacin (0%). Univariate analyses indicated certain diseases, exotic breeds, location, farm size and certain management practices as risk factors for detection of resistance, whereas multivariate analyses showed an association with lumpy skin disease and a protective effect for older animals (\geq 25 months). This study has provided novel insights into the drivers of antibiotic use and their association with antibiotic resistance in an under-studied region of Southern Africa."

Antimicrobial resistance risk factors and characterisation of faecal *E. coli* isolated from healthy Labrador retrievers in the United Kingdom

<https://doi.org/10.1016/j.prevetmed.2015.01.013>

Beyond Antimicrobial Resistance: Evidence for a Distinct Role of the AcrD Efflux Pump in *Salmonella* Biology <https://doi.org/10.1128/mbio.01916-16>

"ABSTRACT For over 20 years, bacterial multidrug resistance (MDR) efflux pumps have been studied because of their impact on resistance to antimicrobials. However, critical questions remain, including why produce efflux pumps under non-antimicrobial treatment conditions, and why have multiple pumps if their only purpose is antimicrobial efflux? *Salmonella* spp. possess five efflux pump families, including the resistance-nodulation-division (RND) efflux pumps. Notably, the RND efflux pump AcrD

has a unique substrate profile, distinct from other *Salmonella* efflux pumps. Here we show that inactivation of *acrD* results in a profoundly altered transcriptome and modulation of pathways integral to *Salmonella* biology. The most significant transcriptome changes were central metabolism related, with additional changes observed in pathogenicity, environmental sensing, and stress response pathway expression. The extent of tricarboxylic acid cycle and fumarate metabolism expression changes led us to hypothesize that *acrD* inactivation may result in motility defects due to perturbation of metabolite concentrations, such as fumarate, for which a role in motility has been established. Despite minimal detectable changes in flagellar gene expression, we found that an *acrD* mutant *Salmonella enterica* serovar Typhimurium isolate was significantly impaired for swarming motility, which was restored by addition of fumarate. The *acrD* mutant outcompeted the wild type in fitness experiments. The results of these diverse experiments provide strong evidence that the AcrD efflux pump is not simply a redundant system providing response resilience, but also has distinct physiological functions. Together, these data indicate that the AcrD efflux pump has a significant and previously underappreciated impact on bacterial biology, despite only minor perturbations of antibiotic resistance profiles. **IMPORTANCE** Efflux pumps in Gram-negative bacteria are studied because of their important contributions to antimicrobial resistance. However, the role of these pumps in bacterial biology has remained surprisingly elusive. Here, we provide evidence that loss of the AcrD efflux pump significantly impacts the physiology of *Salmonella enterica* serovar Typhimurium. Inactivation of *acrD* led to changes in the expression of 403 genes involved in fundamental processes, including basic metabolism, virulence, and stress responses. Pathways such as these allow *Salmonella* to grow, survive in the environment, and cause disease. Indeed, our data show that the *acrD* mutant is more fit than wild-type *Salmonella* under standard lab conditions. We hypothesized that inactivation of *acrD* would alter levels of bacterial metabolites, impacting traits such as swarming motility. We demonstrated this by exogenous addition of the metabolite fumarate, which partially restored the *acrD* mutant's swarming defect. This work extends our understanding of the role of bacterial efflux pumps."

Secrets of the Hospital Underbelly: Patterns of Abundance of Antimicrobial Resistance Genes in Hospital Wastewater Vary by Specific Antimicrobial and Bacterial Family

<https://doi.org/10.3389/fmicb.2021.703560>

"Background: Hospital

wastewater is a major source of antimicrobial resistance (AMR) outflow into the environment. This study uses metagenomics to study how hospital clinical activity impacts antimicrobial resistance genes (ARGs) abundances in hospital wastewater. Methods: Sewage was collected over a 24-h period from multiple wastewater collection points (CPs) representing different specialties within a tertiary hospital site and simultaneously from community sewage works. High throughput shotgun sequencing was performed using Illumina HiSeq4000. ARG abundances were correlated to hospital

antimicrobial usage (AMU), data on clinical activity and resistance prevalence in clinical isolates. Results: Microbiota and ARG composition varied between CPs and overall ARG abundance was higher in hospital wastewater than in community influent. ARG and microbiota compositions were correlated (Procrustes analysis, $p=0.014$). Total antimicrobial usage was not associated with higher ARG abundance in wastewater. However, there was a small positive association between resistance genes and antimicrobial usage matched to ARG phenotype (IRR 1.11, CI 1.06–1.16, $p<0.001$). Furthermore, analyzing carbapenem and vancomycin resistance separately indicated that counts of ARGs to these antimicrobials were positively associated with their increased usage [carbapenem rate ratio (RR) 1.91, 95% CI 1.01–3.72, $p=0.07$, and vancomycin RR 10.25, CI 2.32–49.10, $p<0.01$]. Overall, ARG abundance within hospital wastewater did not reflect resistance patterns in clinical isolates from concurrent hospital inpatients. However, for clinical isolates of the family Enterococcaceae and Staphylococcaceae, there was a positive relationship with wastewater ARG abundance [odds ratio (OR) 1.62, CI 1.33–2.00, $p<0.001$, and OR 1.65, CI 1.21–2.30, $p=0.006$ respectively]. Conclusion: We found that the relationship between hospital wastewater ARGs and antimicrobial usage or clinical isolate resistance varies by specific antimicrobial and bacterial family studied. One explanation, we consider is that relationships observed from multiple departments within a single hospital site will be detectable only for ARGs against parenteral antimicrobials uniquely used in the hospital setting. Our work highlights that using metagenomics to identify the full range of ARGs in hospital wastewater is a useful surveillance tool to monitor hospital ARG carriage and outflow and guide environmental policy on AMR."

Antimicrobial Resistance and Machine Learning: Challenges and Opportunities

<https://doi.org/10.1109/access.2022.3160213> "Antimicrobial Resistance (AMR) has been identified by the World Health Organisation (WHO) as one of the top ten global health threats. Inappropriate use of antibiotics around the world and in particular in Low-to-Middle-Income Countries (LMICs), where antibiotics use and prescription are poorly managed, is considered one of the main reasons for this problem. It is projected that the COVID-19 pandemic will accelerate the threat of AMR due to the increasing use of antibiotics across the world, and especially in countries with limited resources. In recent years, machine learning-based methods showed promising results and proved capable of providing the necessary tools to inform antimicrobial prescription and combat AMR. This timely paper provides a critical and technical review of existing machine learning-based methods for addressing AMR. First, an overview of the AMR problem as a global threat to public health, and its impact on countries with limited resources (LMICs) are presented. Then, a technical review and evaluation of existing literature that utilises machine learning to tackle AMR are provided with emphasis on methods that use readily available demographic and clinical data as well as microbial

culture and sensitivity laboratory data of clinical isolates associated with multi-drug resistant infections. This is followed by a discussion of challenges and limitations that are considered barriers to scaling up the use of machine learning to address AMR. Finally, a framework for accelerating the use of AMR data-driven framework, and building a feasible solution that can be realistically implemented in LMICs is presented with a discussion of future directions and recommendations."

One Health: a multifaceted concept combining diverse approaches to prevent and control antimicrobial resistance <https://doi.org/10.1016/j.cmi.2020.07.012>

The pandemic legacy of antimicrobial resistance in the USA
[https://doi.org/10.1016/s2666-5247\(22\)00227-0](https://doi.org/10.1016/s2666-5247(22)00227-0)

Will the Overuse of Antibiotics During the Coronavirus Pandemic Accelerate Antimicrobial Resistance of Bacteria?

<https://doi.org/10.1097/im9.0000000000000034> "The coronavirus pandemic is one of mankind's biggest challenges of modern day. Viruses can cause deadly pandemics, yet another enemy should not be forgotten: Bacterial pathogens. From a biomedical perspective, bacterial infections should be easier to control, as prokaryotes exhibit structures and biochemical processes that differ from humans, and thus are easier to target. Viruses, however, employ human cells to propagate and are, therefore, more complicated to target by drugs. Until the true dimensions of the current coronavirus pandemic became clear, it felt as though we lived in a world where we could trust that the shelves of pharmaceutical companies would be full with medication to treat almost any human infection. The real challenges for drug development were surely the noncommunicable diseases such as cancer, heart disease, and stroke. These still are the leading causes of death globally, in particular in developed nations, however, while emerging viruses are evermore on our minds, we have to think about another potential apocalypse: Antibiotic-resistant bacteria. Over the decades, and with every successive deployment of a new antibiotic, resistant bacterial strains have emerged; some pathogens are now extensively drug resistant, where an infection might be lethal or at least have a severe impact on morbidity. With the pandemic on our minds, why should we care about antimicrobial resistance (AMR)? Treating severe SARS-CoV-2 infections, physicians often prescribe prophylactic antibiotics.^{1–3} In many countries antibiotic courses are even prescribed to non-hospitalized patients. The rationale behind the decision to deploy prophylaxis is simple: Without antibiotics, the risk of a bacterial infection is drastically increased. Secondary bacterial infections establish easily in patients who suffer from a viral induced infection of the lungs, due to a plethora of reasons, including an altered immune response, reduced clearance of mucus and increased attachment of bacteria to epithelial cells.^{1,2,4} Such infections further reduce the rate of survival.¹ Before SARS-CoV-2, many countries had started programs for antibiotic stewardship under the umbrella of

the "one health" concept, with people, animals, and the environment all interconnected; if we use antibiotics in farming for example, resistance genes can be transferred to human pathogens. Antibiotic stewardship was aimed to reduce the misuse and overuse of antibiotics, and only to treat infections appropriately and where necessary to reduce the rate of development of AMR, thereby preventing the spread of AMR genes. However, these well thought of programs are now at risk of being discontinued under the pressure doctors face during this unprecedented time. Studies summarising published clinical reports show that 60% to 70% of COVID-19 patients had received antibiotics.^{1,5} Depending on the country and the healthcare setting, a maximum of 20% of patients exhibit secondary bacterial or fungal infections.^{1,2} While this indicates that some patients will require antibiotic treatments, the prophylactic use of such drugs is questionable. With tens of millions of people being tested positive for SARS-CoV-2 and possibly millions of fatal cases if current trends continue, antibiotic use in the clinical management of COVID-19 globally will be enormous. The long-term rehabilitation and management of health consequences of COVID-19 are unknown; some individuals may suffer of long term effects such as an impaired lung function, leading to susceptibility to bacterial and fungal infections. Only time will tell, but it is likely that this pandemic and its clinical management will exacerbate the rise of antibiotic resistant superbugs. Now that the coronavirus is here to stay, countries must embrace the concept of antibiotic stewardship even more and do all they can to avoid the emergence and spread of resistant bacteria post-pandemic. Government programs and big pharma will need to commit to supporting these efforts. Up until the 1990s, almost every major pharmaceutical company was developing antibiotics. Most of them, including Bayer, Eli Lilly, and Bristol-Myers Squibb discontinued their antimicrobial R&D efforts over a decade ago. In 2016, a joint declaration issued by over 100 pharmaceutical companies announced the "AMR Industry Alliance." Sadly, within a few years of this declaration the major payers had announced their disengagement in discovery programs in the search for novel antibiotics.^{6,7} New hope has arrived with yet another 360° strategy turn: On the 9th of July, 2020, a consortium that includes Roche, Novartis, GlaxoSmithKline, Bayer Pfizer, Johnson & Johnson, Eli Lilly, Boehringer Ingelheim, and Merck, together with the Wellcome Trust, the WHO, and the European Investment Bank, announced to support the development of two to four novel antibiotics until 2030.⁸ "With the AMR Action Fund, the pharmaceutical industry is investing nearly US\$1 billion to sustain an antibiotic pipeline that is on the verge of collapse, a potentially devastating situation that could affect millions of people around the world," announced Dave Ricks, Chairman and CEO of Eli Lilly who is also the President of the International Federation of Pharmaceutical Manufacturers & Associations. The pledged 1 billion dollars may not go far; the development of a single drug compound costs approximately the same sum.^{9,10}

The successful uptake and sustainability of rapid infectious disease and antimicrobial resistance point-of-care testing requires a complex 'mix-and-match' implementation package <https://doi.org/10.1007/s10096-019-03492-4> "The emergence and spread of antimicrobial resistance is one of the major global issues currently threatening the health and wealth of nations, with effective guidelines and intervention strategies urgently required. Such guidelines and interventions should ideally be targeted at individuals, communities, and nations, requiring international coordination for maximum effect. In this respect, the European Joint Programming Initiative on Antimicrobial Resistance Transnational Working Group 'Antimicrobial Resistance - Rapid Diagnostic Tests' (JPIAMR AMR-RDT) is proposing to consider a 'mix-and-match' package for the implementation of point-of-care testing (PoCT), which is described in this publication. The working group was established with the remit of identifying barriers and solutions to the development and implementation of rapid infectious disease PoCT for combatting the global spread of antimicrobial resistance. It constitutes a multi-sectoral collaboration between medical, technological, and industrial opinion leaders involved in in vitro diagnostics development, medical microbiology, and clinical infectious diseases. The mix-and-match implementation package is designed to encourage the implementation of rapid infectious disease and antimicrobial resistance PoCT in transnational medical environments for use in the fight against increasing antimicrobial resistance."

Non-invasive pneumococcal disease and antimicrobial resistance: vaccine implications <https://doi.org/10.1017/s0950268801006331> "We reviewed laboratory data on non-invasive pneumococcal isolates reported from all diagnostic laboratories in Scotland during the period 1988-99. Of 4491 isolates from hospitalized patients, 654 (64.7%) were from sputum, 79 (7.8%) from the nasopharynx and 278 (27.5%) from other superficial sites. The serogroups included in the 23-valent polysaccharide vaccine caused 96.9% of all non-invasive disease in all age groups. The 7-, 9-, and 11-valent conjugated vaccine serogroups were responsible for 87-94%, 85-93%, 74-81% and 75-84% of non-invasive disease respectively in age groups < 2 years, < or = 5 years, > or = 65 years and all ages. The coverage of non-susceptible penicillin and erythromycin non-invasive isolates was > 99% and > 95% with the 23-valent polysaccharide and 7-11-valent conjugate vaccines respectively. The eight most common serogroups were 23, 9, 6, 19, 14, 3, 15 and 11 (in descending order). The serogroups associated with antimicrobial resistance in non-invasive disease were similar to those found in invasive disease. The finding of a similar serogroup distribution in both invasive and non-invasive disease (regardless of the site of clinical isolate), is consistent with serogroups colonizing non-sterile sites and having the potential to invade. The availability of conjugated vaccines reinforces the importance of systematic surveillance to determine accurately and regularly the coverage of pneumococcal serogroups and types causing both invasive and non-invasive disease."

"Molecular epidemiology and antimicrobial resistance pattern of extended-spectrum- β -lactamase-producing Enterobacteriaceae in Glasgow, Scotland"

<https://doi.org/10.1093/jac/dkr523> "To establish the molecular epidemiology and antimicrobial resistance pattern of extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae harbouring blaCTX-M in Glasgow, Scotland. During a 12 week period, Enterobacteriaceae isolates obtained from urine samples were collected and susceptibility testing performed. Isolates were screened for the presence of blaCTX-M by multiplex PCR and selected Escherichia coli genes were subsequently sequenced. PFGE analysis was performed on selected E. coli isolates in order to identify clonal relationships. There were 155 phenotypically confirmed non-duplicate Enterobacteriaceae isolates obtained from urine samples. blaCTX-M was identified in 131/155 (84.5%) of the ESBL-producing isolates, with CTX-M group 1 enzymes accounting for 103/131 (78.6%) of these. The remaining 24 isolates carried other blaCTX-M types, including CTX-M group 2, CTX-M group 9 and an unidentifiable combination designated CTX-M group G2/Gx. A sample of 46/97 (47.4%) CTX-M-positive E. coli isolates was chosen for PFGE and demographic information regarding the source of the isolates was collated. Eight E. coli clusters were identified by PFGE; however, they did not achieve the 85% cut-off to demonstrate clonality. Nitrofurantoin resistance was significantly greater in the E. coli isolates expressing a non-CTX-M group 1 ESBL when compared with the E. coli isolates expressing a CTX-M group 1 ESBL. As seen in other British studies, blaCTX-M has become the predominant ESBL type in Glasgow, Scotland. The PFGE results show that four different CTX-M groups appear to be circulating in the community and within all four hospitals in the locality. There is little correlation between strain genotype and CTX-M group, thus it is unlikely that cross-infection alone is the driver. It is possible that plasmid migration of CTX-M genes within the E. coli population is occurring."

Antimicrobial resistance in hospital wastewater in Scotland: a cross-sectional metagenomics study [https://doi.org/10.1016/s0140-6736\(19\)32798-9](https://doi.org/10.1016/s0140-6736(19)32798-9)

Antimicrobial Resistance Situational Analysis 2019–2020: Design and Performance for Human Health Surveillance in Uganda <https://doi.org/10.3390/tropicalmed6040178>

"Antibiotic resistance and its mechanisms have been known for over six decades, but global efforts to characterize its routine drivers have only gained momentum in the recent past. Drivers of clinical and community resistance go beyond just clinical practice, which is why one-health approaches offer the most realistic option for controlling antibiotic resistance. It is noteworthy that the emergence of resistance occurs naturally in the environment, but akin to climate change, the current accelerated emergence and spread bears hallmarks of anthropomorphic influence. If left unchecked, this can undo the medical and agricultural advancements of the last century. The WHO recommends that nations develop, adopt, and implement strategies that track the changing trends in antibiotic resistance levels to tackle this problem. This

article examines efforts and progress in developing and implementing a human health antimicrobial resistance surveillance strategy in Uganda. We do so within the context of the National Action Plan for tackling antimicrobial resistance (AMR-NAP) launched in 2018. We discuss the technical milestones and progress in implementing surveillance of GLASS priority pathogens under this framework. The preliminary output of the framework examines the performance and compares AMR and AMU surveillance data to explain observed trends. We conclude that Uganda is making progress in developing and implementing a functional AMR surveillance strategy for human health."

Addressing antimicrobial resistance by improving access and quality of care—A review of the literature from East Africa <https://doi.org/10.1371/journal.pntd.0009529>

"Universal access to healthcare, including quality medicines, is a fundamental human right but is still out of reach for many in low- and middle-income countries (LMICs). An existing framework capturing variability of access to healthcare in low-resource settings includes the 5 dimensions: availability, accessibility, affordability, adequacy, and acceptability. This framework encompasses key components, including health infrastructure and means to access it as well as service organisation, costs, and factors that influence users' satisfaction. However, in reality, the effectiveness of accessed healthcare is measured by the likelihood of a positive outcome. We therefore propose an expansion of this framework to include an additional dimension, ""aspects of quality,"" incorporating quality, which critically influences the ability of the accessed services to generate optimal health outcomes. Within this framework, we explore literature from East Africa likely relevant to a range of LMIC contexts, mainly focusing on the provision of widely used antimicrobials such as antimalarials and antibiotics. We argue that major inadequacies exist across all 6 dimensions of access and quality of drugs and their provision. While the global focus is on curbing excessive antimicrobial use to tackle the antimicrobial resistance (AMR) crisis, major constraints around access shape patients' health-seeking decisions leading to potentially problematic practices that might exacerbate the AMR problem. We advocate for a holistic approach to tackling these inadequacies, encompassing all dimensions of access and quality of healthcare in order to improve health outcomes while simultaneously counteracting the AMR crisis."

Diagnostics and the challenge of antimicrobial resistance: a survey of UK livestock veterinarians' perceptions and practices <https://doi.org/10.1136/vr.105822>

"Background This paper explores the current role and place of diagnostic tests in the treatment of farm animal disease. With the growing focus on reduced reliance on antibiotic medicines in both animal and human patient care, attention is increasingly being focused on the practice, the technology and the function of diagnostic tests and how these can support responsible antimicrobial use. Emerging diagnostic technologies offer the possibility of more rapid testing for bacterial disease, while food chain actors and others are increasingly seeking to make diagnostic tests mandatory

before the use of critically important antibiotics. **Method** This paper reports the findings of a recent large-scale online survey of UK farm animal veterinarians (n=153) which investigated current veterinary diagnostic practice with particular attention to the relationship between diagnostic test use and antibiotic treatment. **Results** Results revealed a range of factors that influence veterinary diagnostic practice and demonstrate the continuing importance of clinical observation and animal/herd knowledge in the selection of antibiotic treatment. **Conclusion** The findings identify a considerable ambivalence on the part of farm animal veterinarians regarding the current and future uses of rapid and point-of-care diagnostic tests as a means of improving clinical diagnosis and addressing inappropriate antibiotic medicine use."

Epigenetic-Mediated Antimicrobial Resistance: Host versus Pathogen Epigenetic Alterations <https://doi.org/10.3390/antibiotics11060809> "Since the discovery of antibiotics, humans have been benefiting from them by decreasing the morbidity and mortality associated with bacterial infections. However, in the past few decades, misuse of antibiotics has led to the emergence of bacterial infections resistant to multiple drugs, a significant health concern. Bacteria exposed to inappropriate levels of antibiotics lead to several genetic changes, enabling them to survive in the host and become more resistant. Despite the understanding and targeting of genetic-based biochemical changes in the bacteria, the increasing levels of antibiotic resistance are not under control. Many reports hint at the role of epigenetic modifications in the bacterial genome and host epigenetic reprogramming due to interaction with resistant pathogens. Epigenetic changes, such as the DNA-methylation-based regulation of bacterial mutation rates or bacteria-induced histone modification in human epithelial cells, facilitate its long-term survival. In this review article, epigenetic changes leading to the development of antibiotic resistance in clinically relevant bacteria are discussed. Additionally, recent lines of evidence focusing on human host epigenetic changes due to the human-pathogen interactions are presented. As genetic mechanisms cannot explain the transient nature of antimicrobial resistance, we believe that epigenetics may provide new frontiers in antimicrobial discovery."

A retrospective analysis of antimicrobial resistance in pathogenic *Escherichia coli* and *Salmonella* spp. isolates from poultry in Uganda

<https://doi.org/10.1080/23144599.2021.1926056> "There are increasing reports of antimicrobial treatment failures for bacterial diseases of poultry in Uganda. The paucity of data on antimicrobial resistance (AMR) of pathogenic bacteria in Uganda is a major setback to AMR control. This study investigated the occurrence of fowl typhoid, colibacillosis, and AMR in associated pathogens from 2012 to 2018. Laboratory records from the Central Diagnostic Laboratory (CDL), a National Veterinary Diagnostic Facility located at Makerere University, were reviewed. Archived isolates of the causative bacteria for the two diseases were also evaluated for AMR. The frequencies of the two disease conditions, their clinical and necropsy presentations and the demographic data

of the diagnostic samples were summarized from the records. Archived bacterial isolates were revived before antimicrobial susceptibility testing. This was done on Mueller Hinton agar using the disk diffusion method, against 16 antimicrobials of medical and veterinary importance according to the Clinical Laboratory Standards Institute guidelines. A total of 697 poultry cases were presented for bacteriological investigations in the review period. Colibacillosis and salmonellosis had prevalence rates of 39.7% (277/697) and 16.2% (113/697), respectively. A total of 63 and 92 isolates of *Escherichia coli* and *Salmonella* spp., respectively, were archived but 43 (68.3%) *E. coli* and 47 (51.1%) *Salmonella* spp. isolates were recovered and evaluated for AMR. Multidrug resistance was more frequent in *E. coli* (38; 88.4%) than salmonellae (25; 53.2%), ($p < 0.001$). The high prevalence of colibacillosis, salmonellosis and the AMR of associated pathogens warrants immediate institution of appropriate disease control measures."

Developing Novel Host-Based Therapies Targeting Microbicidal Responses in Macrophages and Neutrophils to Combat Bacterial Antimicrobial Resistance

<https://doi.org/10.3389/fimmu.2020.00786> "Antimicrobial therapy has provided the main component of chemotherapy against bacterial pathogens. The effectiveness of this strategy has, however, been increasingly challenged by the emergence of antimicrobial resistance which now threatens the sustained utility of this approach. Humans and animals are constantly exposed to bacteria and have developed effective strategies to control pathogens involving innate and adaptive immune responses. Impaired pathogen handling by the innate immune system is a key determinant of susceptibility to bacterial infection. However, the essential components of this response, specifically those which are amenable to re-calibration to improve host defense, remain elusive despite extensive research. We provide a mini-review focusing on therapeutic targeting of microbicidal responses in macrophages and neutrophils to de-stress reliance on antimicrobial therapy. We highlight pre-clinical and clinical data pointing towards potential targets and therapies. We suggest that developing focused host-directed therapeutic strategies to enhance 'pauci-inflammatory' microbial killing in myeloid phagocytes that maximizes pathogen clearance while minimizing the harmful consequences of the inflammatory response merits particular attention. We also suggest the importance of One Health approaches in developing host-based approaches through model development and comparative medicine in informing our understanding of how to deliver this strategy.while minimizing the harmful consequences of the inflammatory response merits particular attention. We also suggest the importance of One Health approaches in developing host-based approaches through model development and comparative medicine in informing our understanding of how to deliver this strategy."

"Antimicrobial resistance in patients with suspected urinary tract infections in primary care in Assam, India" <https://doi.org/10.1093/jacamr/dlab164> "Abstract

Objectives We investigated the prevalence and diversity of antimicrobial resistance in bacteria isolated from urine samples of community-onset urinary tract infection (UTI) patients in southern Assam, India. **Methods** Freshly voided midstream urine samples were collected from patients attending primary healthcare centres, with the patients' epidemiological data also recorded. Species identification was confirmed using a VITEK 2 compact automated system. Phenotypic confirmation of ESBLs was performed using the combined disc diffusion method (CLSI 2017) and carbapenemase production was phenotypically characterized using a modified Hodge test. Common ESBLs and carbapenem-resistance mechanisms were determined in *Escherichia coli* isolates using PCR assays. Incompatibility typing of the conjugable plasmids was determined by PCR-based replicon typing; the phylotypes and MLSTs were also analysed. **Results** A total of 301 (59.7%) samples showed significant bacteriuria along with symptoms of UTI and among them 103 isolates were identified as *E. coli* of multiple STs (ST3268, ST3430, ST4671 and others). Among them, 26.2% (27/103) were phenotypically ESBL producers whereas 12.6% (13/103) were carbapenemase producers. This study describes the occurrence of diverse ESBL genes—*bla*CTX-M-15, *bla*SHV-148, *bla*PER-1 and *bla*TEM—and two *E. coli* isolates carrying the *bla*NDM-1 carbapenemase gene. ESBL genes were located within transconjugable plasmids of IncP and IncF type whereas *bla*NDM-1 was carried in an IncFrepB type plasmid. **Conclusions** This study illustrates the high rate of MDR in *E. coli* causing UTI in primary care in rural Assam. UTIs caused by ESBL- or MBL-producing bacteria are very difficult to treat and can often lead to treatment failure. Thus, future research should focus on rapid diagnostics to enable targeted treatment options and reduce the treatment failure likely to occur with commonly prescribed antibiotics, which will help to combat antimicrobial resistance and the burden of UTIs."

Antimicrobial Resistance Spectrum Conferred by pRErm46 of Emerging Macrolide (Multidrug)-Resistant *Rhodococcus equi* <https://doi.org/10.1128/jcm.01149-21>

"Clonal multidrug resistance recently emerged in *Rhodococcus equi*, complicating the therapeutic management of this difficult-to-treat animal- and human-pathogenic actinomycete. The currently spreading multidrug-resistant (MDR) ""2287"" clone arose in equine farms upon acquisition, and coselection by mass macrolide-rifampin therapy, of the pRErm46 plasmid carrying the *erm*(46) macrolide-lincosamide-streptogramin resistance determinant, and of an *rpoB*S531F mutation. Here, we screened a collection of susceptible and macrolide-resistant *R. equi* strains from equine clinical cases using a panel of 15 antimicrobials against rapidly growing mycobacteria (RGM) and nocardiae and other aerobic actinomycetes (NAA). *R. equi* isolates-including MDR ones-were generally susceptible to linezolid, minocycline, tigecycline, amikacin, and tobramycin according to *Staphylococcus aureus* interpretive criteria, plus imipenem, ceftiofur, and ceftiofur based on Clinical and Laboratory Standards Institute (CLSI) guidelines for RGM/NAA. Susceptibility to ciprofloxacin and moxifloxacin was borderline according to European Committee on Antimicrobial

Susceptibility Testing (EUCAST) criteria. Molecular analyses linked pRErm46 to significantly increased MICs for trimethoprim-sulfamethoxazole and doxycycline, in addition to clarithromycin, within the RGM/NAA panel, and to streptomycin, spectinomycin, and tetracycline resistance. pRErm46 variants with spontaneous deletions in the class 1 integron (C1I) region, observed in $\approx 30\%$ of erm(46)-positive isolates, indicated that the newly identified resistances were attributable to the C1I's sulfonamide (sul1) and aminoglycoside (aaA9) resistance cassettes and adjacent tetRA(33) determinant. Most MDR isolates carried the rpoBS531F mutation of the 2287 clone, while different rpoB mutations (S531L, S531Y) detected in two cases suggest the emergence of novel MDR R. equi strains."

Using 'smart regulation' to tackle antimicrobial resistance in low-income and middle-income countries <https://doi.org/10.1136/bmjgh-2019-001864> "► Low-income and middle-income countries are aligning their National Action Plans on antimicrobial resistance with WHO's 2015 Global Action Plan.► Regulation is a key tool for operationalising national standards aimed at optimising the use of antimicrobial medicines.► On its own, the traditional command-and-control approach to regulation is poorly suited to this challenge.► 'Smart regulation' can be used to supplement, finetune and improve on more traditional regulatory approaches."

"Factors Influencing Antibiotic Prescribing Behavior and Understanding of Antimicrobial Resistance Among Veterinarians in Assam, India"

<https://doi.org/10.3389/fvets.2022.864813> "This study investigates factors influencing veterinarians' antibiotic prescribing behaviors and their understanding of antimicrobial resistance (AMR). The study used a telephone survey of 50 veterinarians conducted in five districts in Assam state, India. The survey sought information on the most prevalent animal diseases, veterinarians' awareness of potential preventive measures, including factors determining antimicrobial prescribing; the types of antimicrobials used for different health conditions in different species, and possible options to reduce antimicrobial use (AMU). The majority (86%) of respondents worked for the government, 98% reported having no written policy for the use of veterinary health products, and 58% have no on-site diagnostic facilities. Ceftriaxone, Enrofloxacin, and Oxytetracycline were the antibiotics (ABX) most frequently prescribed, by 76, 68, and 54% of veterinarians, respectively. These ABX were prescribed mainly for respiratory health problems and mastitis in cattle, and gastrointestinal infections in buffaloes, sheep, goat, and pigs. Severity of clinical symptoms, economic status of the livestock owner, and withdrawal period for ABX were ranked as very important factors for giving ABX. Less than two thirds (64%) were aware of the government ban for Colistin and only 2% were aware of a national plan for AMR. This study highlighted that ABX prescription is mostly based on tentative diagnosis given the lack of diagnostic facilities in most veterinary clinics. There is a need to enhance veterinary healthcare and to improve communication between policy makers and field

veterinarians and, importantly, a need to disseminate clear prescribing guidelines on prudent AMU."

Tackling antimicrobial resistance in primary care facilities across Pakistan: Current challenges and implications for the future <https://doi.org/10.1016/j.jiph.2023.10.046>

"Antibiotics are gradually becoming less effective against bacteria worldwide, and this issue is of particular concern in economically-developing nations like Pakistan. We undertook a scoping review in order to review the literature on antimicrobial use, prescribing, dispensing and the challenges associated with antimicrobial resistance in primary care (PC) settings in Pakistan. Furthermore, this review aims to identify potential solutions to promote appropriate use of antimicrobials in Pakistan. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) checklist, a comprehensive scoping review was conducted to review the literature of antimicrobials used, prescribed and dispensed in PC settings in Pakistan. Google Scholar and Pub-Med were searched for the period 2000-2023. Papers were analyzed on the basis of eligibility i.e., included antimicrobial use, prescribing and dispensing practices by general population at homes, by prescribers in outpatient departments of hospitals and by pharmacists/dispensers in community pharmacies, respectively. Two researchers analyzed the articles thoroughly and disagreements were resolved through discussion with a third reviewer. Both quantitative and qualitative research studies were eligible for inclusion. Additionally, the selected papers were grouped into different themes. We identified 4070 papers out of which 46 studies satisfied our eligibility criteria. The findings revealed limited understanding of antimicrobial resistance (AMR) by physicians and community pharmacists along with inappropriate practices in prescribing and dispensing antibiotics. Moreover, a notable prevalence of self-medication with antibiotics was observed among the general population, underscoring a lack of awareness and knowledge concerning proper antibiotic usage. Given the clinical and public health implications of AMR, Pakistan must prioritize its policies in PC settings. Healthcare professionals (HCPs) need to reduce inappropriate antibiotic prescribing and dispensing, improve their understanding of the AWARe (access, watch and reserve antibiotics) classification and guidance, monitor current usage and resistance trends, as well as implement antimicrobial stewardship (ASP) activities starting in targeted locations."

The dissolvable bead: A novel in vitro biofilm model for evaluating antimicrobial resistance <https://doi.org/10.1016/j.mimet.2017.08.020>

Antimicrobial resistance in animal agriculture: understanding user attitudes and behaviours <https://doi.org/10.1136/vr.j5142>

"Association of health, nutrition, and socioeconomic variables with global antimicrobial resistance: a modelling study" [https://doi.org/10.1016/s2542-5196\(23\)00213-9](https://doi.org/10.1016/s2542-5196(23)00213-9)

"Although antimicrobial use is a key selector for antimicrobial resistance, recent studies have suggested that the ecological context in which antimicrobials are used might provide important factors for the prediction of the emergence and spread of antimicrobial resistance. We used 1547 variables from the World Bank dataset consisting of socioeconomic, developmental, health, and nutritional indicators; data from a global sewage-based study on antimicrobial resistance (abundance of antimicrobial resistance genes [ARGs]); and data on antimicrobial usage computed from the ECDC database and the IQVIA database. We characterised and built models predicting the global resistome at an antimicrobial class level. We used a generalised linear mixed-effects model to estimate the association between antimicrobial usage and ARG abundance in the sewage samples; a multivariate random forest model to build predictive models for each antimicrobial resistance class and to select the most important variables for ARG abundance; logistic regression models to test the association between the predicted country-level antimicrobial resistance abundance and the country-level proportion of clinical resistant bacterial isolates; finite mixture models to investigate geographical heterogeneities in the abundance of ARGs; and multivariate finite mixture models with covariates to investigate the effect of heterogeneity in the association between the most important variables and the observed ARG abundance across the different country subgroups. We compared our predictions with available clinical phenotypic data from the SENTRY Antimicrobial Surveillance Program from eight antimicrobial classes and 12 genera from 56 countries. Using antimicrobial use data from between Jan 1, 2016, and Dec 31, 2019, we found that antimicrobial usage was not significantly associated with the global ARG abundance in sewage ($p=0.72$; incidence rate ratio 1.02 [95% CI 0.92-1.13]), whereas country-specific World Bank's variables explained a large amount of variation. The importance of the World Bank variables differed between antimicrobial classes and countries. Generally, the estimated global ARG abundance was positively associated with the prevalence of clinical phenotypic resistance, with a strong association for bacterial groups in the human gut. The associations between bacterial groups and ARG abundance were positive and significantly different from zero for the aminoglycosides (three of the four of the taxa tested), β -lactam (all the six microbial groups), fluoroquinolones (seven of nine of the microbial groups), glycopeptide (one microbial group tested), folate pathway antagonists (four of five microbial groups), and tetracycline (two of nine microbial groups). Metagenomic analysis of sewage is a robust approach for the surveillance of antimicrobial resistance in pathogens, especially for bacterial groups associated with the human gut. Additional studies on the associations between important socioeconomic, nutritional, and health factors and antimicrobial resistance should consider the variation in these associations between countries and antimicrobial classes. EU Horizon 2020 and Novo Nordisk Foundation."

Epidemiology and Ethics of Antimicrobial Resistance in Animals

https://doi.org/10.1007/978-3-030-27874-8_7 "Abstract Despite a large and rapidly growing volume of research activity and output, primarily on the biological bases of antimicrobial resistance (AMR), epidemiological understanding of the causal mechanisms at play behind the apparent recent global rise in prevalence of AMR has, arguably, progressed very little. Despite this inconvenient fact, political imperative and expedience, among other drivers, have given substantial impetus to an interventionist approach against what are considered to be the culprits for the apparent growing prevalence of AMR and its impacts. Concern about the rise in prevalence of microbial infections that are resistant to therapeutic agents designed to kill them has arisen almost exclusively in relation to human health. (Public awareness and concern about antihelminthic resistance, for which the impacts are much more substantial for animal health, at least in developed temperate countries, are trivial by comparison). Nevertheless, antimicrobial drugs have been, and are, widely used in animal health and production throughout the world, and the contribution of this diverse usage to the 'global AMR problem' has historically been controversial. There is growing acceptance, notwithstanding the limitations in causal understanding noted previously, of AMR as an ecological problem of competing populations of microorganisms experiencing both natural and anthropogenic selection pressures in compartments that transcend species and other boundaries. Typifying what is described as a 'One Health' problem, AMR is therefore considered to be most amenable to conjoint mitigation efforts in all compartments: i.e. interventions in human health, animal health, food and the environment in a coherent manner. In animals, this calls into question the motivations and practices for antimicrobial drug usage, the majority of which are justified on the basis of promoting animal health and welfare and securing a food supply for a growing human population. Not surprisingly, there are great differences in animal husbandry and food demand, and in availability, access and regulation of antimicrobial usage in animals, and in surveillance of AMR, which are likely to be starkest between developed and developing countries. Thus, it is unlikely that the impacts of AMR, and the impacts of efforts to mitigate AMR that are directed to the 'animal compartment' of the ecosystem, will be felt equally across the world."

HAM-ART: An optimised culture-free Hi-C metagenomics pipeline for tracking antimicrobial resistance genes in complex microbial communities

<https://doi.org/10.1371/journal.pgen.1009776> "Shotgun metagenomics is a powerful tool to identify antimicrobial resistance (AMR) genes in microbiomes but has the limitation that extrachromosomal DNA, such as plasmids, cannot be linked with the host bacterial chromosome. Here we present a comprehensive laboratory and bioinformatics pipeline HAM-ART (Hi-C Assisted Metagenomics for Antimicrobial Resistance Tracking) optimised for the generation of metagenome-assembled genomes including both chromosomal and extrachromosomal AMR genes. We demonstrate the

performance of the pipeline in a study comparing 100 pig faecal microbiomes from low- and high-antimicrobial use pig farms (organic and conventional farms). We found significant differences in the distribution of AMR genes between low- and high-antimicrobial use farms including a plasmid-borne lincosamide resistance gene exclusive to high-antimicrobial use farms in three species of *Lactobacilli*. The bioinformatics pipeline code is available at <https://github.com/lkalmar/HAM-ART>."

Advances in Transposon Mutagenesis of *Staphylococcus aureus*: Insights into Pathogenesis and Antimicrobial Resistance

<https://doi.org/10.1016/j.tim.2020.11.003>

"Genomic epidemiology of *Escherichia coli*: antimicrobial resistance through a One Health lens in sympatric humans, livestock and peri-domestic wildlife in Nairobi, Kenya"<https://doi.org/10.1186/s12916-022-02677-7> "Livestock systems have been proposed as a reservoir for antimicrobial-resistant (AMR) bacteria and AMR genetic determinants that may infect or colonise humans, yet quantitative evidence regarding their epidemiological role remains lacking. Here, we used a combination of genomics, epidemiology and ecology to investigate patterns of AMR gene carriage in *Escherichia coli*, regarded as a sentinel organism."

Focussing on resistance to front-line drugs is the most effective way to combat the antimicrobial resistance crisis <https://doi.org/10.1101/498329> "In medical, scientific and political arenas relating to antimicrobial resistance (AMR) there is currently an intense focus on multi-drug resistant pathogens that render last-line antimicrobial treatments ineffective. We question the current emphasis of attention on resistance to last-line antimicrobials, arguing that tackling resistance to front-line antimicrobials has a greater public health benefit. Using AMR monitoring data on 25 drug-pathogen combinations from across Europe, here we show that the presence of front-line pathogen resistance initiates a cascade of resistance selection that ultimately leads to pathogen resistance to last-line antimicrobials. We then interrogate, by modelling the dynamics of resistance evolution, whether 3 key interventions in the strategic response to AMR are more effectively targeted at front-line or last-line treatment. We show that interventions that make front-line therapy more effective by use of antimicrobial adjuvants or front-line resistance diagnostics or by introduction of a novel, front-line antimicrobial all lead to a larger reduction in mortality and morbidity than the same interventions implemented in last-line therapy. Mass use of a newly discovered antimicrobial in front-line infection management to maximise its public health benefit is contrary to current policy but may provide valuable incentives for drug developers. We demonstrate that funding, publications, and attention to those publications do not reflect the importance of front-line antimicrobials and are disproportionately devoted to last-line antimicrobials that account for less than 10% of antimicrobial prescriptions. While studying resistance to last-line drugs is undoubtedly

important, our work relays a strong message to public health agencies, funding bodies, and researchers that allocating resources to front-line infections can be a more effective way to combat the antimicrobial resistance crisis."

Antimicrobial Resistance in the WHO African Region: A Systematic Literature Review 2016–2020 <https://doi.org/10.3390/antibiotics13070659> "Antimicrobial resistance (AMR) is a significant global public health threat. This review presents the most recent in-depth review of the situation of the main AMR types in relation to the most commonly prescribed antibiotics in the World Health Organization (WHO) African Region. Underlying genes of resistance have been analyzed where possible. A search to capture published research data on AMR from articles published between 2016 and 2020 was done using PubMed and Google Scholar, with rigorous inclusion/exclusion criteria. Out of 48003 articles, only 167 were included. Among the tested gram-negative bacteria species,"

Antimicrobial resistance diagnostics: time to call in the young?
[https://doi.org/10.1016/s1473-3099\(16\)30011-1](https://doi.org/10.1016/s1473-3099(16)30011-1)

Are Food Animals Responsible for Transfer of Antimicrobial-Resistant *Escherichia coli* or Their Resistance Determinants to Human Populations? A Systematic Review
<https://doi.org/10.1089/fpd.2017.2411> "The role of farm animals in the emergence and dissemination of both AMR bacteria and their resistance determinants to humans is poorly understood and controversial. Here, we systematically reviewed the current evidence that food animals are responsible for transfer of AMR to humans. We searched PubMed, Web of Science, and EMBASE for literature published between 1940 and 2016. Our results show that eight studies (18%) suggested evidence of transmission of AMR from food animals to humans, 25 studies (56%) suggested transmission between animals and humans with no direction specified and 12 studies (26%) did not support transmission. Quality of evidence was variable among the included studies; one study (2%) used high resolution typing tools, 36 (80%) used intermediate resolution typing tools, six (13%) relied on low resolution typing tools, and two (5%) based conclusions on co-occurrence of resistance. While some studies suggested to provide evidence that transmission of AMR from food animals to humans may occur, robust conclusions on the directionality of transmission cannot be drawn due to limitations in study methodologies. Our findings highlight the need to combine high resolution genomic data analysis with systematically collected epidemiological evidence to reconstruct patterns of AMR transmission between food animals and humans."

"Non-steroidal anti-inflammatory drugs, plant extracts, and characterized microparticles to modulate antimicrobial resistance of epidemic *mecA* positive *S. aureus* of dairy origin" <https://doi.org/10.1007/s13204-020-01628-z>

‘The Mould that Changed the World’: Quantitative and qualitative evaluation of children’s knowledge and motivation for behavioural change following participation in an antimicrobial resistance musical

<https://doi.org/10.1371/journal.pone.0240471> "Background A primary school musical ("The Mould that Changed the World") was developed as a unique public engagement strategy to combat antimicrobial resistance (AMR) by engaging children in the story of the discovery of antibiotics, the risks of drug-resistant infections and the importance of prudent antibiotic use. Methods The musical intervention was implemented in two UK primary schools by music specialists through a series of workshops, associated learning resources and performances to relatives. Participating children (n = 182), aged 9 to 11 years, were given an online questionnaire in the classroom before rehearsals began and at two weeks post-performance with a six-month evaluation in one school. The impact of the musical was analysed using generalised linear models to control for confounding factors. For the qualitative evaluation, fifteen participating children were selected randomly from each school to take part in semi-structured focus groups (n = 5 per group) before rehearsals began and two weeks post-performance. Findings Knowledge gain was demonstrated with children being more likely to answer questions on key messages of the musical correctly at two weeks post- performance (response rate 88%, n = 161) compared with the pre-rehearsal questionnaire (response rate 99%, n = 180) (bacteria can become resistant to antibiotics OR 4.63, C.I. 2.46–9.31 p<0.0001, antibiotic resistant infections can be life threatening OR 3.26 C.I. 1.75–6.32 p = 0.0001, prudent use of antibiotics will slow the rise of antibiotic resistant infections OR 2.16, C.I. 1.39–3.38, p = 0.0006). Long term knowledge gain was demonstrated by a consistent level of correct answers on key messages between two weeks (response rate 95%, n = 89) and 6 months post musical (response rate 71%, n = 67). Following the musical children participating in the focus groups (n = 30) articulated a greater understanding of AMR and the risks of antibiotic overuse. They discussed motivation to minimise personal antibiotic use and influence attitudes to antibiotics in their family and friends. Interpretation This study demonstrates that musical theatre can improve both short and long-term knowledge. It demonstrates a hitherto infrequently reported change in attitude and motivation to change behaviour in children at an influential age for health beliefs. This unique public health tool has the potential for high impact particularly if rolled out within national education programmes for primary school aged children."

System-wide approaches to antimicrobial therapy and antimicrobial resistance in the UK: the AMR-X framework [https://doi.org/10.1016/s2666-5247\(24\)00003-x](https://doi.org/10.1016/s2666-5247(24)00003-x)

"<h2>Summary</h2> Antimicrobial resistance (AMR) threatens human, animal, and environmental health. Acknowledging the urgency of addressing AMR, an opportunity exists to extend AMR action-focused research beyond the confines of an isolated biomedical paradigm. An AMR learning system, AMR-X, envisions a national

network of health systems creating and applying optimal use of antimicrobials on the basis of their data collected from the delivery of routine clinical care. AMR-X integrates traditional AMR discovery, experimental research, and applied research with continuous analysis of pathogens, antimicrobial uses, and clinical outcomes that are routinely disseminated to practitioners, policy makers, patients, and the public to drive changes in practice and outcomes. AMR-X uses connected data-to-action systems to underpin an evaluation framework embedded in routine care, continuously driving implementation of improvements in patient and population health, targeting investment, and incentivising innovation. All stakeholders co-create AMR-X, protecting the public from AMR by adapting to continuously evolving AMR threats and generating the information needed for precision patient and population care."

Emerging Resistance to Empiric Antimicrobial Regimens for Pediatric Bloodstream Infections in Malawi (1998–2017) <https://doi.org/10.1093/cid/ciy834> "The adequacy of the World Health Organization's Integrated Management of Childhood Illness (IMCI) antimicrobial guidelines for the treatment of suspected severe bacterial infections is dependent on a low prevalence of antimicrobial resistance (AMR). We describe trends in etiologies and susceptibility patterns of bloodstream infections (BSI) in hospitalized children in Malawi. We determined the change in the population-based incidence of BSI in children admitted to Queen Elizabeth Central Hospital, Blantyre, Malawi (1998–2017). AMR profiles were assessed by the disc diffusion method, and trends over time were evaluated. A total 89643 pediatric blood cultures were performed, and 10621 pathogens were included in the analysis. Estimated minimum incidence rates of BSI for those ≤ 5 years of age fell from a peak of 11.4 per 1000 persons in 2002 to 3.4 per 1000 persons in 2017. Over 2 decades, the resistance of Gram-negative pathogens to all empiric, first-line antimicrobials (ampicillin/penicillin, gentamicin, ceftriaxone) among children ≤ 5 years increased from 3.4% to 30.2% ($P < .001$). Among those ≤ 60 days, AMR to all first-line antimicrobials increased from 7.0% to 67.7% ($P < .001$). Among children ≤ 5 years, *Klebsiella* spp. resistance to all first-line antimicrobial regimens increased from 5.9% to 93.7% ($P < .001$). The incidence of BSI among hospitalized children has decreased substantially over the last 20 years, although gains have been offset by increases in Gram-negative pathogens' resistance to all empiric first-line antimicrobials. There is an urgent need to address the broader challenge of adapting IMCI guidelines to the local setting in the face of rapidly-expanding AMR in childhood BSI."

"Regulating antimicrobial resistance: market intermediaries, poultry and the audit lock-in" <https://doi.org/10.1007/s10460-023-10525-4> "Abstract Antimicrobial resistance (AMR) has become one of the defining challenges of the twenty-first century. Food production and farming are a key if troubling component of that challenge. Livestock production accounts for well over half of annual global consumption of antimicrobials, though the contribution of the sector to drug resistance is less clear. As a result, there is an injunction to act in advance of incontrovertible evidence for change."

In this paper we engage with the role of market actors in the precautionary regulation of farming practices and AMR threats. The paper takes the UK poultry sector as exemplary of an audit-led process that has, in recent years, achieved impressive reductions in antimicrobial use. Using qualitative interview data with farmers and veterinarians we chart the changing practices that have accompanied this reduction in treatments. We use this analysis to raise some cautions around audit-led systems of regulation. Audits can lock farms and animals into particular versions of farming and animal health; they can elevate harmful compensatory practices (including disinfectant uses); and they can reproduce an actuarial approach to an issue that does not fit the conventions of risk management. The paper presents the considerable successes that have been achieved over a short period of time in a livestock sector, while generating notes of caution concerning the audit-led management of livestock-related AMR threats."

The role of the environment in transmission of antimicrobial resistance between humans and animals: a modelling study <https://doi.org/10.1101/2022.05.19.492687>

"Abstract Background Antimicrobial resistance can be transmitted between animals and humans both directly or indirectly, through transmission via the environment (such as fomites or sewage). However, there is a lack of understanding of, and quantitative evidence about, the contribution of the environment to AMR epidemiology. In this study we incorporate the transmission of resistance via the environment into a mathematical model to study the potential importance of this form of transmission for human resistance levels and any effects of the impact of interventions to reduce antibiotic consumption in animals. Methods We developed a compartmental model of human-animal AMR transmission with an additional environmental compartment. We compared the outcomes of this model under different human-animal-environment transmission scenarios, conducted a sensitivity analysis, and investigated the impact of curtailing antibiotic usage in animals on resistance levels in humans. Results Our findings suggest that human resistance levels are most sensitive to both parameters associated with the human compartment (rate of loss of resistance from humans) and parameters associated with the environmental compartment (rate of loss of resistance from the environment and the transmission rate from the environment to humans). The impact of curtailing antibiotic consumption in animals on long term prevalence of AMR in humans was weaker when environmental transmission was assumed to be high. Conclusions This study highlights that environment-human sharing of resistance can influence the epidemiology of resistant bacterial infections in humans and reduce the impact of interventions that curtail antibiotic consumption in animals. More data on the types and dynamics of resistance in the environment and frequency of human-environment transmission is crucial to understanding the population dynamics of antibiotic resistance."

Global trends in antimicrobial resistance on organic and conventional farms

<https://doi.org/10.1101/2023.04.07.536071>

"ABSTRACT Various

stewardship policies, regulations, and voluntary bans have focused on protecting antimicrobials by limiting their use in livestock. These efforts ignited management shifts ranging from largely nominal (e.g., drugs banned for use as 'growth promoters' were reclassified as 'prophylactic' drugs) to organic farming, which drastically reduces or eliminates use of antimicrobials. Understanding how these farming practices influence the prevalence of antimicrobial resistance in livestock carries important implications for policy makers, public health officials, and farm managers. Here, we reviewed studies spanning the last 20 years to ask if the most stringent effort to reduce antimicrobial use in livestock — organic farming — results in notable reductions in the prevalence of antimicrobial resistance across broad scale geographic ranges, pathogens, and livestock hosts. Our results validate organic farming in reducing the prevalence of antimicrobial resistance (AMR) by ~31.2%, ~26.9%, ~28.2%, ~42.9 and ~36.2% in cattle, chicken, environment, pigs and turkey respectively while also revealing significant variation in the strength of this reduction across contexts. Given that our results join others indicating that AMR is increasing across all types of farms, our results highlight areas where organic farming has been most effective and may provide economical and scalable solutions for farmers."

Threat of Antimicrobial Resistance among Pilgrims with Infectious Diseases during Hajj: Lessons Learnt from COVID-19 Pandemic <https://doi.org/10.3390/antibiotics12081299>

"Hajj pilgrimage is a large mass gathering global event that may facilitate the spread and emergence of various infectious diseases as well as antimicrobial resistance (AMR) in a local and global scenario. Planning and preparing for these public health issues is a challenging and complex process for the Kingdom of Saudi Arabia (KSA) health authorities. Despite multiple efforts for the prevention and treatment of infectious diseases through longtime funding in education and medical care, the prevalence of infectious disease is still high among Hajj pilgrims. The commonly observed infectious diseases during Hajj include respiratory tract infections (influenza and pneumonia), urinary tract infections and skin infections that may necessitate the use of antimicrobials. Beta-lactams are used as a first-line treatment for hospital acquired infections as well as community acquired infections due to their broad-spectrum activity. However, most of the bacterial isolates such as *Staphylococcus* spp., *Pseudomonas* spp. and *E. coli* are resistant to beta-lactams. Irrational use of antimicrobials, lack of infection prevention practices and suboptimal healthcare access further exacerbate the risk of spreading AMR among Hajj pilgrims. Enhanced collaboration between countries, sharing of best practices and international cooperation are crucial in addressing AMR threats among pilgrims. Consequently, robust surveillance systems for early detection and monitoring of AMR, collaboration with national as well as international healthcare agencies, effective infection prevention and control measures, public awareness and rational use of antimicrobials via

antimicrobial stewardship programs are required to mitigate the risk of AMR and ensure the health and well-being of pilgrims during Hajj."

Whole Genome Sequence Analysis Reveals Lower Diversity and Frequency of Acquired Antimicrobial Resistance (AMR) Genes in *E. coli* From Dairy Herds Compared With Human Isolates From the Same Region of Central Zambia

<https://doi.org/10.3389/fmicb.2019.01114> "Antibiotic treatment of sick dairy cattle is critical for the sustainability of this production system which is vital for food security and societal prosperity in many low and middle-income countries. Given the increasingly high levels of antibiotic resistance worldwide and the challenge this presents for the treatment of bacterial infections, the rational use of antibiotics in humans and animals has been emphatically recommended in the spirit of a "One Health" approach. The aim of this study was to characterize antimicrobial resistance (AMR) genes and their frequencies from whole genome sequences of *Escherichia coli* isolated from both dairy cattle and human patients in central Zambia. Whole genome sequences of *E. coli* isolates from dairy cattle (n = 224) and from patients at a local hospital (n = 73) were compared for the presence of acquired AMR genes. In addition we analyzed the publicly available genomes of 317 human *E. coli* isolates from over the wider African continent. Both acquired antibiotic resistance genes and phylogroups were identified from de novo assemblies and SNP based phylogenetic analyses were used to visualize the distribution of resistance genes in *E. coli* isolates from the two hosts. Greater acquired AMR gene diversity was detected in human compared to bovine *E. coli* isolates across multiple classes of antibiotics with particular resistance genes for extended-spectrum beta lactamases (ESBL), quinolones, macrolides and fosfomycin only detected in *E. coli* genomes of human origin. The striking difference was that the Zambian or wider African human isolates were significantly more likely to possess multiple acquired AMR genes compared to the Zambian dairy cattle isolates. The median number of resistance genes in the Zambian cattle cohort was 0 (0-1 interquartile range), while in the Zambian human and wider African cohorts the medians and interquartile ranges were 6 (4-9) and 6 (0-8), respectively. The lower frequency and reduced diversity of acquired AMR genes in the dairy cattle isolates is concordant with relatively limited antibiotic use that we have documented in this region, especially among smallholder farmers. The relatively distinct resistant profiles in the two host populations also indicates limited sharing of strains or genes."

Assignment of virus and antimicrobial resistance genes to microbial hosts in a complex microbial community by combined long-read assembly and proximity ligation

<https://doi.org/10.1101/491175> "Abstract The characterization of microbial communities by metagenomic approaches has been enhanced by recent improvements in short-read sequencing efficiency and assembly algorithms. We describe the results of adding long-read sequencing to the mix of technologies used to assemble a highly complex cattle rumen microbial community, and compare the

assembly to current short read-based methods applied to the same sample. Contigs in the long-read assembly were 7-fold longer on average, and contained 7-fold more complete open reading frames (ORF), than the short read assembly, despite having three-fold lower sequence depth. The linkages between long-read contigs, provided by proximity ligation data, supported identification of 188 novel viral-host associations in the rumen microbial community that suggest cross-species infectivity of specific viral strains. The improved contiguity of the long-read assembly also identified 94 antimicrobial resistance genes, compared to only seven alleles identified in the short-read assembly. Overall, we demonstrate a combination of experimental and computational methods that work synergistically to improve characterization of biological features in a highly complex rumen microbial community."

Resistance to change: AMR gene dynamics on a commercial pig farm with high antimicrobial usage <https://doi.org/10.1038/s41598-020-58659-3> "Group antimicrobial administration is used to control disease in livestock, but we have little insight into how this impacts antimicrobial resistance (AMR) gene dynamics. Here, a longitudinal study was carried out during a single production cycle on a commercial pig unit with high historic and current antimicrobial usage. Quantitative PCR, 16S rRNA gene metabarcoding and shotgun metagenomic sequencing were used to track faecal AMR gene abundance and diversity and microbiome alpha diversity. Shotgun metagenomic sequencing identified 144 AMR genes in total, with higher AMR gene diversity present in young pigs compared to dry sows. Irrespective of in-feed antibiotic treatment or changes in microbiome diversity, mean AMR gene copy number was consistently high, with some AMR genes present at copy numbers comparable to the bacterial 16S rRNA gene. In conclusion, AMR gene prevalence and abundance were not influenced by antibiotic use, either during the production cycle or following whole-herd medication. The high levels of certain genes indicate they are widely disseminated throughout the microbial population, potentially aiding stability. Despite the high and relatively stable levels of resistance genes against the main antimicrobials used, these compounds continue to control production limiting diseases on this unit."

Seasonal Azithromycin Use in Paediatric Protracted Bacterial Bronchitis Does Not Promote Antimicrobial Resistance but Does Modulate the Nasopharyngeal Microbiome <https://doi.org/10.3390/ijms242216053> "Protracted bacterial bronchitis (PBB) causes chronic wet cough for which seasonal azithromycin is increasingly used to reduce exacerbations. We investigated the impact of seasonal azithromycin on antimicrobial resistance and the nasopharyngeal microbiome. In an observational cohort study, 50 children with PBB were enrolled over two consecutive winters; 25/50 at study entry were designated on clinical grounds to take azithromycin over the winter months and 25/50 were not. Serial nasopharyngeal swabs were collected during the study period (12–20 months) and cultured bacterial isolates were assessed for antimicrobial susceptibility. 16S rRNA-based sequencing was performed on a subset of

samples. Irrespective of azithromycin usage, high levels of azithromycin resistance were found; 73% of bacteria from swabs in the azithromycin group vs. 69% in the comparison group. Resistance was predominantly driven by azithromycin-resistant *S. pneumoniae*, yet these isolates were mostly erythromycin susceptible. Analysis of 16S rRNA-based sequencing revealed a reduction in within-sample diversity in response to azithromycin, but only in samples of children actively taking azithromycin at the time of swab collection. Actively taking azithromycin at the time of swab collection significantly contributed to dissimilarity in bacterial community composition. The discrepancy between laboratory detection of azithromycin and erythromycin resistance in the *S. pneumoniae* isolates requires further investigation. Seasonal azithromycin for PBB did not promote antimicrobial resistance over the study period, but did perturb the microbiome."

ONE HEALTH APPROACHES TO TACKLING ANTIMICROBIAL RESISTANCE

<https://doi.org/10.1016/j.soh.2024.100082> "Antimicrobial resistance (AMR) is a significant and growing threat to human health. A recent United Nations General Assembly declaration highlights that those in need must have sustained access to effective treatments. In the absence of a reliable supply of new drugs, pressure on existing drugs can be reduced by minimising demand. Routes to reducing demand include: promotion of WASH (access to clean water, sanitation and hygiene) and Universal Health Coverage (UHC); improved infection control in health care settings; and continued efforts to curtail drug use in agriculture. This is a One Health strategy, requiring coordinated action across the human, livestock and environmental sectors."

Bacterial Resistance to Antimicrobials <https://doi.org/10.1093/jac/dkf056>

"The Mould that Changed the World": a quantitative and qualitative evaluation of knowledge and behavioural change in children in the UK following participation in a musical about antimicrobial resistance [https://doi.org/10.1016/s0140-6736\(19\)32844-2](https://doi.org/10.1016/s0140-6736(19)32844-2)

"CRISPR-Cas Systems in the Fight Against Antimicrobial Resistance: Current Status, Potentials, and Future Directions" <https://doi.org/10.2147/idr.s494327>

"Antimicrobial resistance (AMR) is a critical global health concern that threatens the efficacy of existing antibiotics and poses significant challenges to public health and the economy worldwide. This review explores the potential of CRISPR-Cas systems as a novel approach to combating AMR and examines current applications, limitations, and prospects."

Effect of the duration of antimicrobial exposure on the development of antimicrobial resistance (AMR) for macrolide antibiotics: protocol for a systematic review with a network meta-analysis <https://doi.org/10.1186/s13643-018-0917-0>

"Antimicrobial resistance generates a huge health and economic burden and has

the potential to become the leading cause of death globally, but its underlying drivers are yet to be fully described. The association between a microbe's exposure to antimicrobials and subsequent development of, or selection for, resistance is well documented, as are the exacerbating microbial and human factors. However, the nature and extent of this risk, and how it varies by antimicrobial class and duration of treatment, is poorly defined. The goal of our systematic review and network meta-analysis is to determine the relationship between the duration of antimicrobial exposure and selection for resistance. We will use macrolides as the antimicrobial class of interest and *Streptococcus pneumoniae* carriage as an indicator organism. Our secondary outcomes include duration of symptoms, risk of treatment failure and recurrence, and descriptions of resistance mechanisms. We will conduct a systematic review, selecting studies if they are published randomised controlled trials (RCTs) which report the relationship between taking a macrolide for any indication and incidence of resistant *Streptococcus pneumoniae* in patients of any age group. We will use a predefined search strategy to identify studies meeting these eligibility criteria in MEDLINE, Embase, Global Health and the Cochrane Central Register of RCTs. Two authors will independently screen titles and abstracts, review the full texts and undertake data extraction. We will use the Cochrane Collaboration's tool to assess the quality of included RCTs. If feasible, we will perform pair-wise meta-analysis modelling to determine the relationship between the duration of macrolide treatment and development of macrolide resistant *Streptococcus pneumoniae*. If the identified studies meet the assumptions for a network meta-analysis (NMA), we will additionally model this relationship using indirect comparisons. Our protocol utilises reporting guidance by Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the extensions for protocols (PRISMA-P) and network meta-analyses (PRISMA for NMA). Our review will also report to these standards. Establishing the relationship between the duration of antimicrobial exposure and development of, or selection for, resistance will inform the design of antimicrobial prescriptions, treatment guidelines and the behaviour of both physicians and patients. This work will therefore be a strong contribution towards the full realisation of current antimicrobial resistance stewardship strategies. PROSPERO CRD42018089275"

Interventional research to tackle antimicrobial resistance in Low Middle Income Countries in the era of the COVID-19 pandemic: lessons in resilience from an international consortium <https://doi.org/10.1016/j.ijid.2022.02.013> "This article summarizes the consequences of the COVID-19 pandemic, on an international project to tackle antimicrobial resistance (AMR). The research leadership and process, the access to data, and stakeholders were deeply disrupted by the national and international response to the pandemic, including the interruption of healthcare delivery, lockdowns, and quarantines. The key principles to deliver the research through the pandemic were mainly the high degree of interdisciplinary engagement with

integrated teams, and equitable partnership across sites with capacity building and leadership training. The level of preexisting collaboration and partnership were also keys to sustaining connections and involvements throughout the pandemic. The pandemic offered opportunities for realigning research priorities. Flexibility in funding timelines and projects inputs are required to accommodate variance introduced by external factors. The current models for research collaboration and funding need to be critically evaluated and redesigned to retain the innovation that was shown to be successful through this pandemic."

Author Correction: Genomic analysis of sewage from 101 countries reveals global landscape of antimicrobial resistance <https://doi.org/10.1038/s41467-023-35890-w>

Antimicrobial Usage and Resistance in Makkah Region Hospitals: A Regional Point Prevalence Survey of Public Hospitals <https://doi.org/10.3390/ijerph19010254> "(1) Background: Inappropriate use of antimicrobials and subsequently rise of antimicrobial resistance (AMR) remains a major public health priority. Over-prescribing of broad-spectrum antibiotics is one of the main contributing factors for the emergence of AMR. We sought to describe antimicrobial prescribing trends among patients in public hospitals in Makkah hospitals. (2) Method: We undertook a point prevalence survey (PPS) in six hospitals in Makkah, Saudi Arabia, from January 2019 to July 2019. The survey included all the inpatients receiving antimicrobials on the day of PPS. Data was collected using the Global point prevalence survey (PPS) tool developed by the University of Antwerp, Belgium. (3) Results: Of 710 hospitalized patients, 447 patients (61.9%) were treated with one or more antimicrobials during the study period. The average bed occupancy among six hospitals was 74.4%. The majority of patients received antimicrobials parenterally (90.3%). Of the total prescribed antimicrobials, 415 (53.7%) antimicrobials were used in medical departments, 183 (23.7%) in surgical departments, and 175 (22.6%) in ICUs. Pneumonia (17.3%), skin and soft tissue infections (10.9%), and sepsis (6.6.%) were three common clinical indications. Ceftriaxones were the most commonly used antibiotics that were prescribed in 116 (15%) of patients, followed by piperacillin, with an enzyme inhibitor in 84 (10.9%). (4) Conclusion: There was a high prevalence of antibiotic use in the hospitals of Makkah, which could be a potential risk factor for the incidence of resistant strains, particularly MRSA infection. Public health decision-makers should take these findings into consideration to update national policies for antibiotic use in order to reduce the risks of further increases of AMR."

Changes in resistance among coliform bacteraemia associated with a primary care antimicrobial stewardship intervention: A population-based interrupted time series study <https://doi.org/10.1371/journal.pmed.1002825> "Background Primary care antimicrobial stewardship interventions can improve antimicrobial prescribing, but

there is less evidence that they reduce rates of resistant infection. This study examined changes in broad-spectrum antimicrobial prescribing in the community and resistance in people admitted to hospital with community-associated coliform bacteraemia associated with a primary care stewardship intervention. Methods and findings Segmented regression analysis of data on all patients registered with a general practitioner in the National Health Service (NHS) Tayside region in the east of Scotland, UK, from 1 January 2005 to 31 December 2015 was performed, examining associations between a primary care antimicrobial stewardship intervention in 2009 and primary care prescribing of fluoroquinolones, cephalosporins, and co-amoxiclav and resistance to the same three antimicrobials/classes among community-associated coliform bacteraemia. Prescribing outcomes were the rate per 1,000 population prescribed each antimicrobial/class per quarter. Resistance outcomes were proportion of community-associated (first 2 days of hospital admission) coliform (*Escherichia coli*, *Proteus* spp., or *Klebsiella* spp.) bacteraemia among adult (18+ years) patients resistant to each antimicrobial/class. 11.4% of 3,442,205 oral antimicrobial prescriptions dispensed in primary care over the study period were for targeted antimicrobials. There were large, statistically significant reductions in prescribing at 1 year postintervention that were larger by 3 years postintervention when the relative reduction was -68.8% (95% CI -76.3 to -62.1) and the absolute reduction -6.3 (-7.6 to -5.2) people exposed per 1,000 population per quarter for fluoroquinolones; relative -74.0% (-80.3 to -67.9) and absolute reduction -6.1 (-7.2 to -5.2) for cephalosporins; and relative -62.3% (-66.9 to -58.1) and absolute reduction -6.8 (-7.7 to -6.0) for co-amoxiclav, all compared to their prior trends. There were 2,143 eligible bacteraemia episodes involving 2,004 patients over the study period (mean age 73.7 [SD 14.8] years; 51.4% women). There was no increase in community-associated coliform bacteraemia admissions associated with reduced community broad-spectrum antimicrobial use. Resistance to targeted antimicrobials reduced by 3.5 years postintervention compared to prior trends, but this was not statistically significant for co-amoxiclav. Relative and absolute changes were -34.7% (95% CI -52.3 to -10.6) and -63.5 (-131.8 to -12.8) resistant bacteraemia per 1,000 bacteraemia per quarter for fluoroquinolones; -48.3% (-62.7 to -32.3) and -153.1 (-255.7 to -77.0) for cephalosporins; and -17.8% (-47.1 to 20.8) and -63.6 (-206.4 to 42.4) for co-amoxiclav, respectively. Overall, there was reversal of a previously rising rate of fluoroquinolone resistance and flattening of previously rising rates of cephalosporin and co-amoxiclav resistance. The limitations of this study include that associations are not definitive evidence of causation and that potential effects of underlying secular trends in the postintervention period and/or of other interventions occurring simultaneously cannot be definitively excluded. Conclusions In this population-based study in Scotland, compared to prior trends, there were very large reductions in community broad-spectrum antimicrobial use associated with the stewardship intervention. In contrast, changes in resistance among coliform bacteraemia were more modest. Prevention of resistance through judicious use of new

antimicrobials may be more effective than trying to reverse resistance that has become established."

Characterization of Extended Spectrum Beta-Lactamases (ESBL) Producing
Escherichia coli Isolates from Surface Water Adjacent to Pharmaceutical
Industries in Bangladesh: Antimicrobial Resistance and Virulence Pattern
<https://doi.org/10.48022/mbl.2305.05006>

Health systems appraisal of the response to antimicrobial resistance in low- and middle-income countries in relation to COVID-19: Application of the WHO building blocks <https://doi.org/10.1111/1758-5899.13262> "Abstract COVID-19 has inflicted both beneficial and damaging effects on health systems responding to antimicrobial resistance (AMR). Data shows that the positive impacts of the pandemic (including enhanced hygiene, mask wearing and widespread use of personal protective equipment), are likely to have been overshadowed by the negative effects: emerging AMR pathogens and mechanisms; further outbreaks and geographic spread of AMR to non-endemic countries; rising infections from multidrug-resistant pathogen; an overall higher burden of AMR. The multisectoral complexities of AMR and the totality of health systems challenge our ability to understand the impact of the COVID-19 pandemic on country responses to AMR. In this analysis, we synthesise international evidence characterising the role of the pandemic on the six key building blocks of health systems in responding to AMR across low- and middle-income countries (LMICs). We apply systems thinking within and between the building blocks to contextualise the impact of one pandemic on another."

A review of the predictors of antimicrobial use and resistance in European food animal production <https://doi.org/10.3389/frabi.2023.1209552> "Antimicrobial resistance (AMR) is a major threat to global health and a key One Health challenge linking humans, animals, and the environment. Livestock are a key target for moderation of antimicrobial use (AMU), which is a major driver of AMR in these species. While some studies have assessed AMU and AMR in individual production systems, the evidence regarding predictors of AMU and AMR in livestock is fragmented, with significant research gaps in identifying the predictors of AMU and AMR common across farming systems. This review summarizes existing knowledge to identify key practices and critical control points determining on-farm AMU/AMR determinants for pigs, layer and broiler hens, beef and dairy cattle, sheep, turkeys, and farmed salmon in Europe. The quality and quantity of evidence differed between livestock types, with sheep, beef cattle, laying hens, turkeys and salmon underrepresented. Interventions to mitigate both AMU and/or AMR highlighted in these studies included biosecurity and herd health plans. Organic production typically showed significantly lower AMU across species, but even in antibiotic-free systems, varying AMR levels were identified in livestock microflora. Although vaccination is frequently implemented as part of herd health

plans, its effects on AMU/AMR remain unclear at farm level. Social and behavioral factors were identified as important influences on AMU. The study fills a conspicuous gap in the existing AMR and One Health literatures examining links between farm management practices and AMU and AMR in European livestock production."

Combining antibiotics to tackle antimicrobial resistance

<https://doi.org/10.1038/s41564-025-01969-x>

Conference report of the 2024 Antimicrobial Resistance Meeting

<https://doi.org/10.1038/s44259-024-00058-z> "The Antimicrobial Resistance - Genomes, Big Data and Emerging Technologies Conference explored key topics including measuring the burden of AMR, global public health pathogen genomics infrastructure and surveillance, translation and implementation of genomics for AMR control, use of techniques such as wastewater surveillance, mathematical and statistical modelling, and Artificial Intelligence (AI) to aid understanding of AMR. This report describes research presented during plenary sessions and discussions, keynote presentations and posters."

Pangenomic analysis of *Staphylococcus pseudintermedius* to better understand antimicrobial resistance profiles <https://doi.org/10.1099/acmi.ac2019.po0562>

"Although *Staphylococcus pseudintermedius* are commensal bacteria of dogs, they are also opportunistic pathogens, being the primary cause of canine skin and ear infections. Recently, more attention has been given to this species, due to the emergence of antimicrobial resistance. Further to this a methicillin resistant *S. pseudintermedius* was isolated from a human and was subsequently found to be multidrug resistant. To better understand the frequency of carriage of antimicrobial resistance, as well as the presence of multidrug resistance, we examined the pangenome of over 200 *S. pseudintermedius* isolates from across the globe. Focussing on methicillin resistance we were able to identify staphylococcal cassette chromosome *mec* (SCC*mec*) types unique to specific Bayesian Analysis of Population Structure (BAPS) groups, including groups which carried *mec* resistance genes independent of a known SCC*mec* element. In addition, we identified an SCC*mec* element, within isolates from North America, that shares 99 % nucleotide identity with a recently described non-typeable SCC*mec* element carried by *Staphylococcus aureus* isolated from a human in the Netherlands. Beyond methicillin resistance we found over 50 % of those strains analysed were putatively multidrug resistant (resistant to 3 or more antimicrobial drug classes). This highlights the diverse resistance determinants present in animal staphylococci and the importance of monitoring *S. pseudintermedius*."

Assessing the impact of antimicrobial resistance policies on antibiotic use and antimicrobial resistance-associated mortality in children and adults in low and middle-income countries: a global analysis <https://doi.org/10.1136/bmjph-2023-000511>

"Introduction Antimicrobial resistance (AMR) poses a major threat to global

health security today. In recent years, many low and middle-income countries (LMICs) have implemented policies to optimise antibiotic use in both formal and informal healthcare settings. However, there is limited evidence on the effectiveness of these national efforts in LMICs. **Methods** We investigated the empirical relationship between national policies aimed at restricting antibiotic use and actual antibiotic consumption in 138 LMICs. Data on national policies were obtained from the Tripartite AMR Country Self-Assessment Survey (TrACSS) as well as from the Global Survey of Experts on AMR (GSEAR). Seven independent variables relating to AMR policies were evaluated. Outcomes included the proportion of children receiving antibiotics for lower respiratory tract infections and diarrhoea (specific to paediatric populations), along with total antibiotic consumption and AMR-associated mortality in general populations. **Results** Our analysis of 138 LMICs found wide variation in antibiotic use between countries and regions. We observed strong evidence of negative association (mean difference MD=-0.150, 95% CI (-0.2593 to -0.0407)) between the presence of regulatory or legislative policies that ban over-the-counter sales of antibiotics and the proportion of children receiving antibiotic drugs for lower respiratory tract infection. Furthermore, stronger AMR governance was associated with reduced total antibiotic consumption at the country level (MD=-1.259, 95% CI (-2.297 to -0.2216)). No associations were found between other policy variables and antibiotic use or mortality. **Conclusion** The results presented here suggest that there is some evidence of an empirical relationship between national policies aimed at limiting over-the-counter antibiotic sales and actual antibiotic usage practices. Further policy effectiveness research will be needed to better understand the true impact of government measures. In general, a multifaceted approach will likely be needed to fight AMR and preserve antibiotics' effectiveness, including evidence-based policies, targeted education and research."

Antimicrobial Resistance Gene Profiles in Communities Selected with Novel and Previously Encountered Antibiotics <https://doi.org/10.54254/2753-8818/2025.20458>

"Antibiotics are extensively employed worldwide for therapeutic purposes, often leading to overuse, which constitutes a contributing factor to the emergence of antibiotic resistance (ABR). This phenomenon arises from diminished effectiveness of antibiotics in treating bacterial infections due to resistance development. However, limitations in experimental conditions and equipment making it challenging to pinpoint the precise sources of antibiotic resistance, consequently constraining the breadth of research on ABR. Genomic analysis of antibiotic-resistant bacteria assists in unveiling the origins and pathways of resistance dissemination. This study employs Nanopore-based metagenomic sequencing, enabling direct sequencing of microbial DNA within macrogenomic samples, thereby yielding comprehensive sequence data. Coupled with qPCR and 16S rRNA gene datasets, this approach facilitates the exploration of antibiotic resistance gene distribution and prevalence within microbial communities across different environments Focusing on microbial communities within Scottish farmlands,

isolated colonies were exposed to antibiotics (sulfamonomethoxine and erythromycin) for several weeks. By comparing them to untreated control group microorganisms, the identification of antibiotic resistance genes (ABRGs), along with their variations in prevalence and abundance, aims to analyse the impact of these two antibiotics on these species."

Secrets of the hospital underbelly: patterns of abundance of antimicrobial resistance genes in hospital wastewater vary by specific antimicrobial and bacterial family

<https://doi.org/10.1101/19006858> "ABSTRACT Background Hospital wastewater is a major source of antimicrobial resistance (AMR) outflow into the environment. This study uses metagenomics to study how hospital clinical activity impacts antimicrobial resistance genes (ARGs) abundances in hospital wastewater. Methods Sewage was collected over a 24-hour period from multiple wastewater collection points representing different specialties within a tertiary hospital site and simultaneously from community sewage works. High throughput shotgun sequencing was performed using Illumina HiSeq4000. ARG abundances were correlated to hospital antimicrobial usage (AMU), data on clinical activity and resistance prevalence in clinical isolates. Results Microbiota and ARG composition varied between collection points and overall ARG abundance was higher in hospital wastewater than in community influent. ARG and microbiota compositions were correlated (Procrustes analysis, $P = 0.014$). Total antimicrobial usage was not associated with higher ARG abundance in wastewater. However, there was a small positive association between resistance genes and antimicrobial usage matched to ARG phenotype (IRR 1.11, CI 1.06 - 1.16, $P < 0.001$). Furthermore, analysing carbapenem and vancomycin resistance separately indicated that counts of ARGs to these antimicrobials were positively associated with their increased usage (carbapenem rate ratio (RR) 1.91, 95% confidence intervals (CI) 1.01 – 3.72, $P = 0.07$, and vancomycin RR 10.25, CI 2.32 – 49.10, $P < 0.01$). Overall, ARG abundance within hospital wastewater did not reflect resistance patterns in clinical isolates from concurrent hospital inpatients. However, for clinical isolates of the family Enterococcaceae and Staphylococcaceae, there was a positive relationship with wastewater ARG abundance (odds ratio (OR) 1.62, CI 1.33 – 2.00, $P < 0.001$, and OR 1.65, CI 1.21 – 2.30, $P = 0.006$ respectively). Conclusions We found that the relationship between hospital wastewater ARGs and antimicrobial usage or clinical isolate resistance varies by specific antimicrobial and bacterial family studied. One explanation we consider is that relationships observed from multiple departments within a single hospital site will be detectable only for ARGs against parenteral antimicrobials uniquely used in the hospital setting. Our work highlights that using metagenomics to identify the full range of ARGs in hospital wastewater is a useful surveillance tool to monitor hospital ARG carriage and outflow and guide environmental policy on AMR."

Correction to: The rumen microbiome as a reservoir of antimicrobial resistance and pathogenicity genes is directly affected by diet in beef cattle

<https://doi.org/10.1186/s40168-019-0764-9> "Following publication of the original article [1], the authors reported an error in the Additional file 1."

The antibiotic procurement saga: a long-neglected stewardship target to combat antimicrobial resistance in Pakistan <https://doi.org/10.1186/s13756-025-01521-w>

‘The Mould that Changed the World’: Quantitative and Qualitative Analysis of Knowledge and Behavioural Change following Participation in an Antimicrobial Resistance Musical <https://doi.org/10.1099/acmi.fis2019.po0032> "Background: Antimicrobial resistance (AMR) is driven by antimicrobial exposure. Engaging the general public with this issue is vital in order to shape attitudes and change behaviour. A primary school musical (‘The Mould that Changed the World’) was developed as a novel educational strategy with the explicit aim of engaging the public in the fight against AMR. Methods: The musical was implemented in two primary schools as workshops followed by public performances. There were 166 child participants aged 9 to 11 years. Quantitative data was collected through a classroom questionnaire before the musical, two weeks after, and six months after. Qualitative data were collected through children’s focus groups before the musical and two weeks after. Results: Knowledge of the key messages of the musical had increased two weeks after the musical (proportion test, 0.65, 0.77, $p < 0.001$) and this gain in knowledge was sustained six months later (proportion test, 0.65, 0.82, $p < 0.001$). Children recognised factors contributing to AMR, felt empowered to change their own health behaviours and demonstrated antimicrobial stewardship with intention to reduce antibiotic use. They suggested the musical had stimulated discussion around these topics at home. The musical was perceived as an enjoyable and memorable way to learn about AMR. Conclusion: This study demonstrates potential for the use of musical theatre in this field as a novel device to improve long-term knowledge, change attitudes and emotionally engage the general public through children. Alongside existing interventions, it represents a further unique and valuable tool in the fight against AMR."

Assessing the Associations between Antimicrobial Resistance Policies and Antibiotic Use in Low and Middle Income Countries: A Global Analysis

<https://doi.org/10.2139/ssrn.4506558> "Background: Antimicrobial resistance (AMR) poses a major threat to global health security today. In recent years, many low- and middle-income countries (LMICs) have implemented new policies to optimize antibiotic use in both formal and informal healthcare settings. However, there is limited evidence on the effectiveness of these national efforts. Methods: We investigated the empirical relationship between national policies aimed at restricting antibiotic use and actual antibiotic consumption in 138 LMICs. Data on national policies were obtained

from the Tripartite AMR Country Self-Assessment Survey (TrACSS) as well as from the Global Survey of Experts on AMR (GSEAR). Seven independent variables pertaining to AMR policies were evaluated. Outcomes were the proportion of children receiving antibiotics for the treatment of lower respiratory tract infections and diarrhoea as well as total antibiotic consumption and mortality associated with antimicrobial-resistant infections. Results: Our analysis of 138 LMICs found wide variation in antibiotic use between countries and regions. We observed a significant negative association (mean difference MD = -0.150, 95% CI [-0.2593, -0.0407]) between the presence of regulatory or legislative policies that ban over-the-counter sales of antibiotics and the proportion of children under five receiving antibiotic drugs for lower respiratory tract infection. Furthermore, stronger AMR governance was associated with reduced overall antibiotic consumption at the country level (MD = -1.259, 95% CI [-2.297, -0.2216]). No associations were found between other policy variables and antibiotic use or mortality. Interpretation: The results presented here suggest that the empirical relationship between national policies designed to limit over-the-counter antibiotic sales and actual antibiotic practices is weak. Further policy effectiveness research will be needed to better understand the lacking impact of government measures. More generally, a multifaceted approach will likely be needed to fight AMR and preserve antibiotics' effectiveness, including evidence-based policies, targeted education, and research. Funding: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 801076, through the SSPH+ Global PhD Fellowship Programme in Public Health Sciences (GlobalP3HS) of the Swiss School of Public Health. Declaration of Interest: All authors declare no conflicts of interest. Ethical Approval: This study was reviewed and approved by Ethics Committee Northwest and Central Switzerland (EKNZ) according to HRA Art.51 (Statement ID: AO_2020_00026)."

HAM-ART: An optimised culture-free Hi-C metagenomics pipeline for tracking antimicrobial resistance genes in complex microbial communities

<https://doi.org/10.1101/2021.08.16.456459> "Abstract Shotgun

metagenomics is a powerful tool to identify antimicrobial resistance (AMR) genes in microbiomes but has the limitation that extrachromosomal DNA, such as plasmids, cannot be linked with the host bacterial chromosome. Here we present a laboratory and bioinformatics pipeline HAM-ART (Hi-C Assisted Metagenomics for Antimicrobial Resistance Tracking) optimised for the generation of metagenome-assembled genomes including both chromosomal and extrachromosomal AMR genes. We demonstrate the performance of the pipeline in a study comparing 100 pig faecal microbiomes from low- and high-antimicrobial use pig farms (organic and conventional farms). We found significant differences in the distribution of AMR genes between low- and high-antimicrobial use farms including a plasmid-borne lincosamide resistance gene exclusive to high-antimicrobial use farms in three species of *Lactobacilli*. Author

Summary Antimicrobial resistance (AMR) is one of the biggest global health threats humanity is facing. Understanding the emergence and spread of AMR between different bacterial species is crucial for the development of effective countermeasures. In this paper we describe a user-friendly, affordable and comprehensive (laboratory and bioinformatics) workflow that is able to identify, associate and track AMR genes in bacteria. We demonstrate the efficiency and reliability of the method by comparing 50 faecal microbiomes from pig farms with high-antibiotic use (conventional farms), and 50 faecal microbiomes from pig farms with low-antibiotic use (organic farms). Our method provides a novel approach to resistance gene tracking, that also leads to the generation of high quality metagenomic assembled genomes that includes genes on mobile genetic elements, such as plasmids, that would not otherwise be included in these assembled genomes."

Opportunities and challenges in antimicrobial resistance policy including animal production systems and humans across stakeholders in Argentina: a context and qualitative analysis <https://doi.org/10.1136/bmjopen-2023-082156> "Introduction Gaps in antimicrobial resistance (AMR) surveillance and control, including implementation of national action plans (NAPs), are evident internationally. Countries' capacity to translate political commitment into action is crucial to cope with AMR at the human–animal–environment interface. Methods We employed a two-stage process to understand opportunities and challenges related to AMR surveillance and control at the human–animal interface in Argentina. First, we compiled the central AMR policies locally and mapped vital stakeholders around the NAP and the national commission against bacterial resistance. Second, we conducted qualitative interviews using a semistructured questionnaire covering stakeholders' understanding and progress towards AMR and NAP. We employed a mixed deductive–inductive approach and used the constant comparative analysis method. We created categories and themes to cluster subthemes and determined crucial relationships among thematic groups. Results Crucial AMR policy developments have been made since 1969, including gradually banning colistin in food-producing animals. In 2023, a new government decree prioritised AMR following the 2015 NAP launch. Our qualitative analyses identified seven major themes for tackling AMR: (I) Cultural factors and sociopolitical country context hampering AMR progress, (II) Fragmented governance, (III) Antibiotic access and use, (IV) AMR knowledge and awareness throughout stakeholders, (V) AMR surveillance, (VI) NAP efforts and (VII) External drivers. We identified a fragmented structure of the food production chain, poor cross-coordination between stakeholders, limited surveillance and regulation among food-producing animals and geographical disparities over access, diagnosis and treatment. The country is moving to integrate animal and food production into its surveillance system, with most hospitals experienced in monitoring AMR through antimicrobial stewardship programmes. Conclusion AMR accountability should involve underpinning collaboration at different

NAP implementation levels and providing adequate resources to safeguard long-term sustainability. Incorporating a multisectoral context-specific approach relying on different One Health domains is crucial to strengthening local AMR surveillance."

Antimicrobial resistance profiles and molecular epidemiology of *Klebsiella pneumoniae* isolates from Scottish bovine mastitis cases

<https://doi.org/10.1017/s0950268824001754> "Klebsiella pneumoniae are opportunistic pathogens which can cause mastitis in dairy cattle. K. pneumoniae mastitis often has a poor cure rate and can lead to the development of chronic infection, which has an impact on both health and production. However, there are few studies which aim to fully characterize K. pneumoniae by whole-genome sequencing from bovine mastitis cases. Here, K. pneumoniae isolates associated with mastitis in dairy cattle were identified using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) and whole-genome sequencing. Furthermore, whole-genome sequence data were used for phylogenetic analyses and both virulence and antimicrobial resistance (AMR) prediction, in parallel with phenotypic AMR testing. Forty-two isolates identified as K. pneumoniae were subject to whole-genome sequencing, with 31 multi-locus sequence types being observed, suggesting the source of these isolates was likely environmental. Isolates were examined for key virulence determinants encoding acquired siderophores, colibactin, and hypermucoidy. The majority of these were absent, except for ybST (encoding yersiniabactin) which was present in six isolates. Across the dataset, there were notable levels of phenotypic AMR against streptomycin (26.2%) and tetracycline (19%), and intermediate susceptibility to cephalixin (26.2%) and neomycin (21.4%). Of importance was the detection of two ESBL-producing isolates, which demonstrated multi-drug resistance to amoxicillin-clavulanic acid, streptomycin, tetracycline, cefotaxime, cephalixin, and cefquinome."

"Engaging rural communities in Bangladesh to tackle antimicrobial resistance through the Community Dialogue Approach: a process evaluation protocol for COSTAR project in Cumilla, Bangladesh" <https://doi.org/10.3389/fpubh.2024.1466780>

"Introduction Antimicrobial resistance (AMR) is a global problem and is especially threatening for low-and-middle income countries like Bangladesh. The COSTAR (Community-led Solutions to Antimicrobial Resistance) project includes a Randomised Control Trial (RCT) which aims to evaluate the effectiveness of the Community Dialog Approach (CDA) to improve levels of correct and appropriate knowledge and reported practice about antibiotics, antibiotic use, and antibiotic resistance (ABR) from a One Health perspective, among adult community members in 5 selected sub-districts of Cumilla. The CDA is a community engagement approach involving community members in active discussions also known as Community Dialogs (CD), run by local facilitators. The dialogs promote collective action to produce sustainable social change. The trial's process evaluation will evaluate fidelity, dose,

adaptation, reach, mechanisms of impact and the process of knowledge diffusion using the MRC framework for the evaluation of complex interventions. Methods and analysis The process evaluation will be implemented in the catchment areas of 25 selected community clinics (CCs) in the intervention group. The key actors involved in the process evaluation are participants from master trainers and trainers training; community dialog facilitators; supervisors; community dialog participants and non-participants; and local and national level government stakeholders. Qualitative and quantitative data will be collected through Focus Group Discussion (FGDs); Case Studies; Key Informant Interview (KIIs); CD observations; monitoring forms; quarterly feedback from facilitators and supervisors, and pre-and-post-test questionnaires administered during the training of facilitators. All qualitative data will be coded using a priori coding framework in NVIVO 14. Quantitative data will be analysed using descriptive statistics. Ethics and dissemination Ethical approval was obtained from the Bangladesh Medical Research Council (BMRC): BMRC/NREC/2019–2022/427 and from the University of Leeds Faculty of Medicine and Health ethics board: MREC 20–034. All results will be disseminated through a one pager summary; infographics; peer-reviewed journal articles and national and international conferences. Clinical trial registration <https://www.isrctn.com/ISRCTN93756764> , identifier ISRCTN93756764."

Understanding the interests of academics from diverse disciplines to identify the prospective focus for a UK-based transdisciplinary network involving farm-to-fork stakeholders on antimicrobial resistance in agrifood systems: An online survey <https://doi.org/10.1016/j.onehlt.2024.100884> "Antimicrobial resistance (AMR) evolution and onward transmission of resistance genes is impacted by interrelated biological and social drivers, with evidence and impacts observed across human, animal and environmental One Health domains. Systems-based research examining how food production impacts on AMR in complex agrifood systems is lacking, with little written on management approaches in the UK that might prevent and respond to this challenge. One approach is the creation of a transdisciplinary network to enhance capacity, capability and collaboration between agrifood-focused disciplines and stakeholders. This co-creation platform for network-wide systems-based activities would reduce inefficiencies in AMR-related activities around agrifood, providing a cross-cutting, cohesive community to deliver transformational guidance on relevant, practical agrifood solutions that add value by reducing AMR, antimicrobial usage and associated costs, and decreasing resultant environmental contamination by prioritising challenges, sharing knowledge and best practice, and co-creating practical solutions with key stakeholders. An online survey determined prospective network focus, structure and priorities, with responses analysed using mixed methods. Survey results suggested respondents have interests in synthesising data using systems-approaches and using certain disciplines such as 'social sciences' within network activities. There were disconnects in how and whom to work with on this, with generalised use of 'social

science/scientists' but lack of disciplinary understanding (e.g., anthropology, sociology) suggesting disciplinary differences awareness-training is useful. A similar generalisation is seen for mathematics/statistics. There are strong interests in working with food system practitioners (e.g., farmers/vets), providing opportunities for farm/field visits/knowledge exchange, and human health, reflecting the need for farm-to-fork understanding of impacts. There were notable mentions of policy/governance, emphasising translational research desires to create meaningful change. Disciplines/fields did not always align with identified interests e.g., systems and implementation science, suggesting the utility of network activity around introducing these disciplines e.g., methodology-focused rather than subject-focused conferences exploring lateral thinking about subjects. We suggest starting by developing understanding of the most important research questions by working with stakeholders, then working back to how we would achieve desirable project outcomes and who else is needed for this."

Boston: mechanisms of antimicrobial drug resistance

<https://doi.org/10.1093/jac/6.3.303>

Resisting the resistance. Is there progress in maintaining antimicrobial efficacy?

<https://doi.org/10.1002/9781119278368.ch7.3> "The major health threat caused by multiple drug resistance affecting both human and animal welfare, and the anticipation there will be limited future availability of new antibiotics, particularly in veterinary medicine. Moxifloxacin, similar to pradofloxacin in veterinary medicine, is one of the key antimicrobials used in *Streptococcus pneumoniae* infections in human medicine. The drug has been on the market since 2000 in North America, and no changes to *S. pneumoniae* susceptibility to this antimicrobial have been seen. This indicates that the antimicrobial is adequately dosed for this particular organism and has the right mechanisms for treating this particular organism to reduce selective pressure and resistance development. Work in recent years has aimed to assess the influence of the number of infectious organisms on antimicrobial susceptibility and resistance. This chapter discusses the risks associated with use and/or abuse of antimicrobial treatment. It also talks about the use of probiotics and faecal microbiota transplantation (FMT)."

Editorial: Molecular mechanisms of resistance to "last resort" antimicrobials in

Enterobacterales <https://doi.org/10.3389/fcimb.2024.1429200> "EDITORIAL article Front. Cell. Infect. Microbiol., 30 May 2024Sec. Bacteria and Host Volume 14 - 2024 | <https://doi.org/10.3389/fcimb.2024.1429200>"

Farm-level drivers of antimicrobial use and resistance in livestock: An evidence synthesis <https://doi.org/10.1016/j.anscip.2023.01.387>

Antimicrobial Blue Light Reduces Human-Wound Pathogens' Resistance to Tetracycline-Class Antibiotics in Biofilms <https://doi.org/10.3390/cells14030219>

"Biofilms contribute to chronic infections and the development of antimicrobial resistance (AMR). We are developing an antimicrobial blue light (aBL) device to reduce bacterial bioburden in wounds and decrease reliance on systemic antibiotics. aBL induces the generation of reactive oxygen species (ROS) through photoexcitation of endogenous chromophores, causing bacterial damage and death. This study explores the combination of tetracyclines (TCs) with aBL for the treatment of biofilm infections in vitro. Tetracyclines (TCs), including second-generation minocycline (MC), doxycycline (DOCT), and third-generation agents omadacycline (OM) and tigecycline (TG), were evaluated for their ability to enhance bactericidal effects and ROS production during aBL treatment of abiotic biofilm. TCs were tested under dark conditions and with varying aBL light parameters against biofilms of methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* (PA), and *Escherichia coli* (E. coli). Results showed that TCs alone were ineffective against these biofilm cultures. However, when combined with aBL either before or after TC treatment, significant enhancement of microbicidal activity was observed. When the aBL is added before the TCs, there was equivalent bactericidal effect, indicating that TCs primary action against biofilms were not as photosensitizers. These findings suggest that aBL can significantly enhance the antimicrobial activity of TCs, potentially offering a new effective approach to treating biofilm-associated infections and combating AMR when aBL is applicable."