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GAMRIF Global AMR Innovation Fund

UKaid from the British people

AMR Reseach Landscape: A Gap Analysis Study

January 2023

Contents

Abbreviations

AI	Artificial Intelligence
AM	Antimicrobial
AMIS	Antimicrobials in Society
AMR	Antimicrobial Resistance
APHA	Animal and Plant Health Agency
API	Active Pharmaceutical Ingredient
ARB	Antibiotic-Resistant Bacteria
ARGs	Antibiotic Resistance Genes
AST	Antimicrobial Susceptibility Testing
BMGF	Bill and Melinda Gates Foundation
CAIs	Community-Acquired Infections
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Africa Centres for Disease Control and Prevention
CHAI	Clinton Health Access Initiative
CRO	Contract Research Organisation
DEFRA	UK Department for Environment, Food and Rural Affairs
DHSC	UK Department for Health and Social Care
DNDi	Drugs for Neglected Diseases initiative
EDL	Essential Diagnostics List
EML	Essential Medicines List
ESBL	Extended Spectrum Beta-Lactamase
EU	European Union
FAO	Food and Agriculture Organization
FEND-TB	Feasibility of Novel Diagnostics for TB
FIND	Foundation for Innovative New Diagnostics
GAFFI	Global Action For Fungal Infections
GAMRIF	Global Antimicrobial Resistance Innovation Fund
GARDP	Global Antibiotic Research and Development Partnership
GAVI	Gavi, The Vaccine Alliance
GBD	Global Burden of Disease
GLASS	Global Antimicrobial Resistance Surveillance System
GRAM	Global Research on Antimicrobial Resistance
HAI	Hospital-Acquired Infections
IPC	Infection Prevention and Control
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
HIC	High Income Countries
LMIC	Low- and Middle-Income Country
MAP	Micro-Array Patches
MDR	Multi-Drug Resistant
MPP	Medicines Patent Pool
NAP	National Action Plan
OECD	Organisation for Economic Cooperation and Development
OMV	Outer Membrane Vesicles
PDP	Product Development Partnership
POC	Point of Care
PPL	Priority Pathogen List
PQP	Prequalification of Medicines Programme
RTI	Respiratory Tract Infections
SDG	Sustainable Development Goal
STI	Sexually Transmitted Infection
TB	Tuberculosis
TPP	Target Product Profile
TrACSS	Tripartite AMR Country Self-Assessment Survey
TRL	Technology Readiness Level
UTI	Urinary Tract Infection
VIPS	Vaccine Innovation Prioritisation Strategy
WASH	Water, Sanitation and Hygiene
WGS	Whole Genome Sequencing
WHO	World Health Organization
WWTP	Wastewater Treatment Plants
WOAH	World Organisation for Animal Health

Acknowledgements and disclaimer

Acknowledgements

The lead authors of this report are Cheri Grace (Lead Expert), Adriana Rodriguez (Project Manager and Senior Researcher), Panos Deoudes (Researcher) and Sophia Stone (Researcher).

Disclaimer

This research is funded by the UK Department of Health and Social Care as part of the Global AMR Innovation Fund (GAMRIF). This is a UK aid programme that supports early-stage innovative research in underfunded areas of antimicrobial resistance (AMR) research and development for the benefit of those in low- and middle-income countries (LMICs), who bear the greatest burden of AMR. The views expressed in this report are those of the authors and not necessarily those of the UK Department of Health and Social Care.

Executive summary

The Global Antimicrobial Resistance Innovation Fund (GAMRIF) was originally conceived as a GBP 50 million Research and Development (R&D) programme designed to tackle drug resistance in low- and middle-income countries (LMICs). GAMRIF aims to achieve this goal through targeting neglected areas of antimicrobial resistance (AMR) research, building partnerships with industry, governments, and global organisations, and raising additional funding. In September 2021, Ecorys was contracted by the Department of Health and Social Care (DHSC) to conduct a gap analysis of the current AMR R&D landscape to identify emerging challenges and opportunities in AMR research. The gap analysis intended to help GAMRIF make evidence-based funding decisions and identify potential areas for future GAMRIF interventions. The gap analysis covered six study areas: diagnostics, therapeutics, and vaccines ("human health"), and plants, environmental contamination, and animal health. The gap analysis involved six steps including a review of the literature, 36 stakeholder interviews, and an expert survey (n= 55). The current report provides the results, findings and observations of the gap analysis.

Summary of findings: Human health

Evidence-informed decision making: There remain substantial gaps in population-based data on the burden of AMR, as well as in information around transmission dynamics. The development pipeline of technologies could be further enhanced, and existing technologies could be adapted for LMICs. There is a need for field validation work to determine how best to integrate new technologies into LMIC health systems, and to demonstrate economic utility to justify uptake of approaches. In terms of data availability, there is good data on the vaccines pipeline (e.g., Wellcome), and on the treatment pipeline (e.g., WHO), and fair data on the diagnostic pipeline (e.g., FIND). There are some remaining gaps in data, particularly on i) substandard/falsified medicines, mapping its correlation to AMR patterns, and ii) on antifungal resistance. Finally, evidence highlighted the need for better data sharing within and between countries.

Enabling environment: More than 80% of AMR R&D funding goes to human health, with the top three research categories funded being basic research, therapeutics, and operational R&D. A large portion of AMR R&D funding originates in high -income countries (HICs) and remains in HICs. USD 0.9 billion out of USD 8.9 billion total AMR R&D goes to LMIC-specific R&D.[1] In terms of human health financing, very little is being done in LMICs on product-related R&D (such as diagnostics and vaccines).There has been good progress in building the architecture for coordinating and managing pipelines for technology readiness level (TRL) progression, through Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), Global Antibiotic Research & Development Partnership (GARDP) and others. More R&D focused on new technologies for product development needs to be conducted in LMICs, where there is also a need for clinical trial network capacity strengthening and harmonisation in diagnostics regulation, to reduce the costs of conducting numerous field trials. GARDP and the Wellcome Trust are developing a clinical trial network capacity in LMICs, with the aim of reducing costs and increasing the speed of trials. In vaccines, there is a need for more investment into new AMR R&D platform technologies.

Diagnostic innovation and access: Tertiary healthcare is dominated by a few suppliers of existing technologies, who set prices, while suppliers of existing technologies at the local and community levels are more scattered. Innovation challenge funds (e.g., Longitude Prize) have been fuelling the pipeline, with FIND and CARB-X enabling TRL progression. R&D for new tools is required, with the key needs being Point of Care (POC) diagnostics for sepsis, STIs and pneumonia, and a viral versus bacterial diagnostic test or even a bacterial/non-bacterial test. Market shaping work is needed to improve access to existing diagnostics (both bacterial and fungal), while the main priority is operational research to introduce and scale already existing fungal-relevant diagnostics. On the demand side, there have been consultations to try and ascertain how and whether different types of tests might be used in different healthcare settings. Diagnostics represent a considerable expense, and their "use case" in LMICs is not always clear. Supply-side investment incentives will be needed

[1]The Global AMR R&D Hub (2021): Annual Report 2021: The Global AMR R&D Funding Landscape and interviwees with AMR R&D hub team

until and unless there is a clear answer as to who/when to test, and the value of the test. There are remaining gaps on the demand side in terms of connecting R&D more to LMIC-contexts.

Therapeutic innovation and access: There has been some progress in therapeutics, notably through the activity of CARB-X and others' grants and fellowships. The R&D pipeline has diversified, including more funding to antibiotic alternatives and preventatives, including through GAMRIF and the Bill and Melinda Gates Foundation (BMGF) support to CARB-X. However scientific challenges remain largely unresolved, e.g., understanding under what circumstances clinically relevant resistance mutations arise. Continued R&D is needed, since pathogens that have a serious health impact in LMICs (e.g., *Salmonella typhi*), have hardly any promising drug candidates in the pipeline. There is also a significant barrier for LMICs to access existing treatments due to high pricing, lack of supply, few paediatric formulations and limited market shaping work to address these challenges. Similarly, there is insufficient access to first-line antifungals and also an increasing burden of antifungal resistance. As a result, efforts need to focus on pairing increased antifungal access with increased antifungal diagnostics. There has been some work to support increased access to existing antibiotics through paediatric reformulation work and the nascent SECURE initiative.

Vaccine innovation and access: Significant progress has been made in the development and access to vaccines, but LMICs still struggle with access to the most basic vaccinations due to their poor overall health systems, insufficient supply chains, and inadequate data management systems. R&D challenges that are hindering the contribution of vaccines towards AMR include technological complexity, limited consideration of impact of future vaccines on AMR, and the balance between developing new vaccines versus increasing the reach and/or repurposing existing ones. However, substantial progress has been made in three areas: availability of existing vaccines and evidence showing their impact on decreasing AMR prevalence, the use of novel technologies and approaches, and the development of new vaccines against pathogens on the WHO priority pathogen list. New ways to administer and deliver vaccines have been developed (e.g., micro-array patches). There is still a substantial need to invest in: operational research aimed at increasing uptake of existing vaccines, early-stage research for high-impact pathogens with unclear R&D feasibility, AMR studies that investigate pathogens for which the value of vaccine development is unclear and repurposing of existing vaccines and increasing access through further supply availability and developing vaccines that target Hospital-Acquired Infections (HAI).

Summary of findings: Plants, environment and animal health

Evidence-informed decision making: Research shows that human activities cause high concentrations of Antibiotic-Resistant Bacteria (ARB) and genes in the environment, while contamination from farm run-offs is mainly driven by antimicrobials in animals, crops, and fish feed. Transmission pathways are now widely accepted but there is uncertainty on several factors. In terms of plants, antimicrobials are commonly used as pesticides and their overuse and/or misuse can lead to development and spread of AMR, mainly through food and waste.[2] Lack of data has been highlighted as the crucial challenge in this area with insufficient understanding of the scale or the potential consequences.[3] Evidence showed that many countries do not have surveillance programmes that will provide the necessary evidence, more so in relation to plants than human and animal health.[4] Data is also scarce for animal health, although it is now recognised that livestock accounts for the majority of global antibiotic consumption, up to 80%. Data collation is incomplete and of low quality, as there are no appropriate and standardised monitoring systems in place, with this affecting evidence-based decision making. Efforts are being made by experts at the country and global levels to define and recommend "acceptable" levels of antimicrobial concentrations in discharges. There have been some positive advances in data collection for animal health. The Antimicrobials in Society (AMIS) Antimicrobial Use Tracker allows longitudinal analysis of global/local trends in antimicrobial use data in non-hospital settings from LMICs and HICs. New data is being submitted and analysed to improve understanding by the WOAH. There are still major knowledge gaps around AMR in the plants/environment and animals in LMICs, as well as gaps in measures to monitor antimicrobial usage patterns to aid decision making. Capacity building and local investment in data collection is a key priority area. Other areas to explore

[2] Wellcome (2018): Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges
[3] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps
[4] Ibid

include bottom-up and top-down data sharing and research on human behaviour and factors influencing decision making around antimicrobial use in farm settings.

Enabling environment: A crucial challenge in plant/environment/animal AMR R&D is the lack of funding. Only 3% of total AMR R&D funding goes to environment and plant research, while 6% is allocated to animal health.[5] Most of the funding related to LMICs does not go to research institutions in those countries but to HICs, which can lead to interventions and approaches that cannot be fully translated to an LMIC context. In addition, there is no regulation or standards nor data collection on wastewater limits for antimicrobials. In terms of progress, awareness of AMR in the environment and animal sectors has been rising at the global level, although at a slower rate for plants. Awareness and knowledge-raising activities have been rolled out in several countries and, on the regulatory side, progress has been reported towards greater conformity with international benchmarks, for example in "safe limits" in antimicrobial discharges. Additionally, some multinational pharmaceutical companies also require their LMIC-based API suppliers to follow targets on discharge limits.[6] Overall, the main gaps identified were around the availability and focus of new funding, applying regulations where possible, raising awareness, and positively influencing social and behaviour change. Creating an enabling environment would require provision of behaviour change alternatives and incentives, effective awareness raising approaches through training and workshops, communications, and low-cost, accessible technology.

Innovations and interventions: One of the major challenges in environmental AMR is the lack of evidence to develop targeted and evidence-based interventions, especially in LMICs. Interventions can be complicated to design and implement as they need to address multiple pathways to contamination. There are also challenges in the effectiveness and uptake of existing interventions for environment/plant/animals, particularly due to the difficulties in transferring interventions from HICs to LMICs, where socioeconomic factors are a crucial determinant (e.g., affecting uptake of crop protection alternatives). Progress has been made in environment/plant health in adopting preventative measures to reduce AMR in both waste and drinking water. Newly developed mitigation strategies include pesticide management systems and innovative water treatment plant solutions. Progress has also been made in animal health, although this is limited to antimicrobial peptides, phages, and yeast. Gaps remain in adapting HIC solutions to LMIC contexts and the need to further integrate environmental and animal AMR interventions within broader health/WASH programmes (as most are currently standalone AMR-only interventions). Interventions can include low-cost, accessible, and innovative technologies in animal diagnostics, antimicrobial alternatives, greater uptake of vaccines, and testing potentially counterfeit or mis-labelled products.

Conclusions and observations

Significant evidence gaps exist across all study areas: this represents one of the most significant challenges in implementing LMIC-appropriate interventions.

Need for operational research to reduce AMR in LMICs: innovations and effective interventions exist in HICs but are not always feasible to adapt in LMIC settings.

Gaps in regulation and compliance: further research needs to be conducted to assess the feasibility and cost considerations of regulatory measures in LMICs.

Need for better, global, and harmonised surveillance: more openly available data and data sharing across countries can enable further R&D on AMR solutions.

Need for R&D for new technical solutions with relevance to LMIC settings: there is a need to increase the quantity and innovative quality of the R&D pipeline targeting pathogens, syndromes and target product profiles (TPP) that meet LMIC needs.

Need to raise awareness about AMR, especially in plants/environment and animal health: more efforts in this area would be beneficial towards preventing/tackling AMR.

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[5] The Global AMR R&D Hub (2021): Annual Report 2021: The Global AMR R&D Funding Landscape and interviewees with AMR R&D hub team

[6] Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021

Need for late-stage R&D/market shaping to support introduction and scaling of improved technologies: more work needs to be done to facilitate product adaptation, commercialisation, introduction, and scaling of technologies relevant to AMR.

Lack of funding especially in environment and animal health: more funding is needed to prioritise LMIC-appropriate innovations and solutions to tackle AMR.

Integrating AMR solutions within broader health and WASH programmes: combining/integrating interventions can strengthen the current evidence base and leverage current budgets to provide efficient solutions for LMICs.

Socioeconomic factors play a crucial role in the current AMR landscape in LMICs: social behaviour change communication interventions and raising awareness at all levels could be greatly beneficial.

Clinical trial network capacity strengthening improvements: these improvements could reduce cost and speed up the development on diagnostic, therapeutics, and vaccines in LMICs.

1.0 Introduction

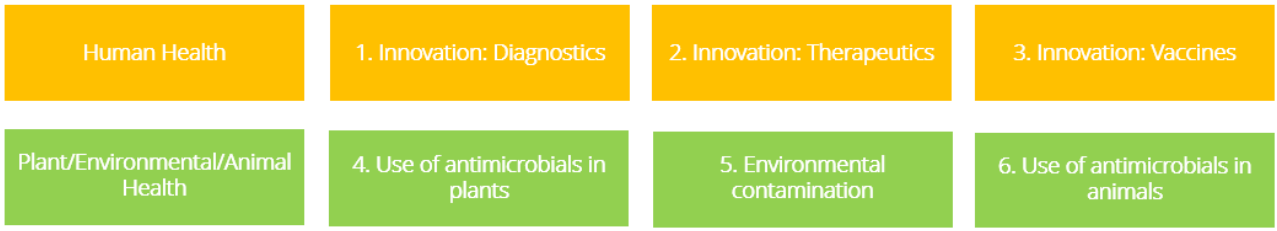
1.1 Purpose and scope of the gap analysis

Following a competitive tender process, Ecorys was appointed by the Department for Health and Social Care (DHSC) in September 2021 to conduct a gap analysis of the Antimicrobial Resistance (AMR) research and development (R&D) landscape to identify underfunded areas in AMR research. The gap analysis intends to help the Global Antimicrobial Resistance Innovation Fund (GAMRIF) make evidence-based funding decisions and examines potential areas for future GAMRIF interventions. DHSC requested that the research should focus on the following two research questions:

- What areas of AMR R&D that could most benefit Low- and Middle-Income Countries (LMICs) are neglected and underfunded?
- In which areas of AMR R&D could future GAMRIF funds have the most impact?

The gap analysis covers six study areas. Figure 1 is clustered into two groups: i) human health (divided by diagnostics, vaccines and therapeutics) and ii) plant, environmental and animal health. Some relevant areas for AMR R&D were outside the scope of the work, as they were less fitting with GAMRIF's theory of change (ToC). There were also inevitably resource limitations to this work (see Service Description Annex 1). Due to these two limitations, it is possible that the gaps identified are not an exhaustive reflection of important needs in AMR R&D.

Figure 1: Study areas



Source: Own analysis, 2021

2.0 Gap analysis findings

In line with our research framework, findings on human and plant/environment/animal health are presented across three main categories – evidence-informed decision making, enabling environment, and innovation/access of interventions – with each covering challenges, progress, and gaps. Due to similarities in the findings these categories were aggregated across three human health technologies under 'evidence-informed decision making' and under 'the enabling environment'. Findings on technological innovations and advancements for diagnostics, therapeutics and vaccines are wide ranging and specific to these areas, thus 'innovation/access interventions' for diagnostics, therapeutics and vaccines are discussed in separate sections, 2.3, 2.3 and 2.5 respectively.

2.1 Human health: Evidence-informed decision making

2.1.1 Challenges

The Review on AMR provided an estimate of the AMR burden which has been widely publicised[7]; however, the AMR community has lacked more detailed and comprehensive population-based AMR burden data by region and pathogen. Evidence is also lacking on transmission dynamics – the various parameters that influence the expansion of AMR – as well as on the effectiveness of new tools in reducing AMR, for example, through quantifying the impact on AMR resulting from increases in global immunisation.

In terms of technology, some reviews have been undertaken to understand the pipeline stage/proximity to market of various diagnostics, therapeutics, and vaccine technologies, and to specify R&D candidate target product profiles (TPP). However, the pipeline of technologies that are currently under development is not sufficient to meet existing needs.[8] There is still a need to invest in R&D to develop new and improved diagnostics, therapeutics, and vaccine technologies. Existing technologies could be adapted for use in LMICs. Additionally, the utility and value proposition of some new tools is not always clear to LMIC decision-makers, especially for diagnostics and therapeutic alternatives used as preventatives since these would entail an additional cost above the use of antibiotics.

2.1.2 Progress

On burden of disease, the Global Antimicrobial Resistance Surveillance System (GLASS) has been set up by the World Health Organization (WHO) to monitor AMR trends, with 73 countries participating. Data published in The Lancet by the Global Research on Antimicrobial Resistance Project (GRAM)[9] has provided a much more nuanced picture on the burden of disease, including by pathogen type and by region. The GRAM work examined syndromes, pathogens and pathogen-drug combinations associated with and attributed to bacterial AMR, including by Global Burden of Disease (GBD) defined regions. Overall, lower respiratory tract infections (RTI) were the highest burden infectious syndrome and *Escherichia coli* as the leading pathogen, while the pathogen-drug combination, methicillin-resistant *Staphylococcus aureus* causes the highest number of deaths attributable to bacterial AMR. Resistance to fluoroquinolones and β-lactam antibiotics (e.g., carbapenems, cephalosporins and penicillin), which are common first-line therapy for severe infections, accounted for more than 70% of deaths attributable to AMR.

All six leading pathogens contributing to the burden of AMR are on the WHO Priority Pathogens List (PPL)[10], although only one (*Streptococcus pneumoniae*) has been the focus of a major global health intervention programme, primarily through pneumococcal vaccination. The work carried out to develop the WHO PPL confirmed that the highest burden of AMR is in resource-poor settings. A surprise finding was the particularly high AMR burden in sub-Saharan Africa; even though resistance prevalence is lower in this region than in other regions, the rate of deaths in which infection plays a role is higher. Another unexpected finding was the high burden of carbapenem-resistant *Acinetobacter baumannii* in

[7] Tackling drug-resistant infections globally: final report and recommendations/the Review on Antimicrobial Resistance (2016)
[8] WHO (2020): 2019 antibacterial agents in clinical development: An analysis of the antibacterial clinical development pipeline
[9] Antimicrobial Resistance Collaborators (2022): Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis
[10] WHO (2020): 2019 antibacterial agents in clinical development: An analysis of the antibacterial clinical development pipeline

South Asia and other LMICs. The highest burden pathogens in sub-Saharan Africa differed depending on the level of income in regions; half of the AMR-attributable mortality in high-income regions is linked to *S. aureus* and *E. coli*, whereas in sub-Saharan Africa the main causes of AMR-attributable deaths are *Streptococcus pneumoniae* and *Klebsiella pneumoniae* (16% and 20% of AMR deaths respectively).

On understanding the technology pipeline landscape and prioritising R&D, the WHO has developed several tools to guide funders of antibiotic R&D towards prioritising the biggest unmet global health needs. These tools include the Priority Pathogens List from 2017[11] which lists four TPP (for four novel antibiotics, addressing enteric fever, gonorrhoea, neonatal sepsis, and urinary tract infections (UTIs)) describing the optimal and minimum required characteristics of end products, as well as frequent pipeline analyses. In addition, there are clear WHO criteria for therapeutic innovation (new class, new molecular target, new mode of action, no cross-resistance with existing drug classes). These tools and criteria make clear what the focus should be to achieve success. WHO has also published TPPs for LMIC-relevant diagnostics, specifying price, level of health system use, pathogen specificity, and accuracy/sensitivity. WHO Essential Medicines List (EML)[12] and Essential Diagnostics List (EDL)[13] now include technologies relevant to fungal disease with work having been carried out on an antifungal Priority Pathogen List (PPL)[14].

Various studies[15,16] have proposed a target number of new therapeutics and aggregate R&D funding requirements to ensure sustainable impact on AMR.[17] There is good data available on candidates in the vaccines R&D pipeline (Wellcome[18]); good data available on the treatment pipeline (WHO[19], PEW[20], AMR Benchmark[21], Unitaid[22] and others), and fair data available on the diagnostic pipeline (Foundation for Innovative New Diagnostics (FIND)[23], Unitaid, AMR Benchmark). Scoping is continual, for example Unitaid will commission a full landscaping of sexually transmitted infection (STI) diagnostics in the development pipeline in 2022[24].

2.1.3 Gaps related to evidence-informed decision making in human health innovation and access

Although data on LMIC burden is improving, notably through GRAM and GLASS work[25], there are remaining gaps, including i) the need for better data on substandard/falsified medicines, mapping its correlation to AMR patterns and ii) a need for better data on antifungal resistance, which was not surveyed in the GRAM publication in The Lancet. The GRAM work also now needs to be translated into changes in location-specific policy decisions, including those related to Infection Prevention and Control (IPC), access to essential antibiotics and R&D focus. The WHO priority list, which is intended to direct R&D efforts, only includes five of the seven pathogen-drug combinations that were found to cause the most deaths attributable to AMR in the recent The Lancet publication, with Multi-Drug Resistant (MDR) tuberculosis (TB) and fluoroquinolone-resistant *E. coli* not being included. Also, methicillin-resistant *S. aureus* – the leading pathogen-drug combination for attributable deaths is listed as a "high" and not "critical" priority. The WHO pathogen list does not yet

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[11] Ibid
[12] World Health Organisation (2019): Model List of Essential Medicines.
[13] World Health Organisation (2021): The selection and use of essential in vitro diagnostics.
[14] Ibid
[15] Tackling drug-resistant infections globally: final report and recommendations/the Review on Antimicrobial Resistance (2016)
[16] http://drive-ab.eu/
[17] The ONeill UK Review on AMR made initial recommendations in 2015, stating that a USD 2 billion early-stage innovation fund should be established to "cover the blind spots left by the current level and structure of grant funding." The Boston Consulting Group, in a report commissioned by the German Government, issued a similar recommendation shortly thereafter for the creation of a fund with an annual budget of 200 million USD over ten years. Since then, about one third of that has been mobilised (e.g. through CARB-X in the U.S., and the Novo Repair Impact Fund)
[18] Wellcome and Boston Consulting Group (2018): Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities, Wellcome (2020): The Global Response to AMR: Momentum
[19] WHO (2019): Technical consultation on in vitro diagnostics for AMR, 27–28 March 2019, WHO Headquarters, Geneva: Meeting report
[20] https://www.pewtrusts.org/en/trend/archive/summer-2016/the-global-threat-of-antimicrobial-resistance
[21] AMR Industry Alliance (2018): Tracking progress to address AMR
[22] Unitaid (2017): Unitaid's Work in AMR
[23] https://www.finddx.org/amr/
[24] Interview with Unitaid
[25] World Health Organisation (2020: Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report

consider new estimates of the global burden of specific pathogen–drug combinations included in the Lancet publication, which states that *S. aureus* is a major global health threat and a critical pathogen for the global health community.

On the technology side, TPPs have been developed to coalesce R&D activity around priority needs and there is relatively good intelligence on the status of technology candidates in the upstream R&D pipeline. However, information is not as robust when it comes to i) understanding which existing technologies (diagnostics or therapeutics) could be adapted, or market shaped[26] and ii) the framing/positioning of new diagnostics and therapeutics within LMIC healthcare delivery systems. Several stakeholders also suggested that more work could be done to refine/nuance the WHO diagnostic TPPs, looking at what is needed for different syndromes and at different levels of the health system. Finally, there is a need to conduct more field validation work, to determine how best to integrate new technologies into LMIC health systems, and a need to conduct modelling work, to demonstrate economic utility especially for diagnostics and preventatives (vaccines and antibiotic alternatives) which require an additional expense above antibiotics.

Two other needs emphasised by interviews related to data, are:

- Data sharing between countries, as part of a pandemic preparedness system. This is challenged by/linked to regulatory barriers.
- More and better data is required on the impact of vaccines on AMR, that is, how immunisation reduces disease burden and therefore the need for antimicrobial use and, ultimately, the transmission of drug-resistant pathogens.

There is not uniform agreement that spending on R&D for therapeutics, diagnostics and vaccines is the best way to reduce AMR burden in LMICs. Many interviewees said that IPC and water sanitation and hygiene (WASH) interventions (including innovations related to technical infection control solutions) could be better adopted as well as water and sanitation engineering innovations, and that these would be more transformative in addressing AMR in LMICs. The recent GRAM publication in The Lancet similarly concluded that, "Community based programmes are particularly important in LMICs where the AMR burden is highest and clean water and sanitation infrastructure is weak." However, recent comprehensive reviews of low-cost WASH interventions typical of those often featured in policy and programs in rural settings in low-income countries (LICs)[27] were not shown to be associated with improvements in health outcomes. Experts conclude that "transformative WASH" or WASH+ is needed (meaning WASH interventions that are multi-faceted, more comprehensive, and more ambitious).[28]

2.2 Human health: Enabling environment

2.2.1 Challenges

The Global AMR R&D Hub's most recent report concludes that public and philanthropic investment in AMR R&D specifically increased between 2017 and 2019. More than 80% of AMR R&D funding goes to human health, and the top three research categories funded across all sectors are Basic Research, Therapeutics, and Operational R&D. When viewed

[26] Market shaping refers to strategies and actions that seek to change market dynamics in markets that do not function well, towards objectives of increasing access to safe, effective and affordable health products (such as vaccines, medicines or diagnostics) in LMICs. In well-functioning markets, supply meets demand; products are of high quality and available presentations meet country preferences; supply is consistent, timely and reliable as regulatory processes are efficient and potential risks related to individual suppliers are minimised; manufacturers have resources, information and incentives to overcome barriers to enter and compete in the market; customers consider cost comprehensively, that is, beyond price per unit; and product innovation is incentivised. Underpinning these attributes is a clear flow of information between stakeholders that conveys reasonable certainty around demand, supply, and cost to all parties involved. (reference: Gavi's Supply and Procurement Strategy 2016-2021). Successful market shaping employs interventions that optimise the existing organisation and functions in the market, or the incentives and risks of key market players. Financial instruments are used, such as "push" funding to reduce costs and offset risks of R&D, "pull" funding (such as through procurement approaches, market guarantees or advance purchases), as well as analytical tools such as market studies and demand forecasting, and programmatic tools like technical assistance to countries to support product introduction processes.

[27] Such as interventions to increase chlorination of drinking water at the point-of-use; to increase access to, and use of, 'improved' pit latrines, including the safe disposal of child faeces; and to increase handwashing with soap by providing 'handwashing stations' with an ongoing supply of soap

[28] See i) Cumming, O., et al. (2019): The implications of three major new trials for the effect of water, sanitation and hygiene on childhood diarrhea and stunting: A consensus statement, and ii) Pickering, A., et al. (2019): The WASH Benefits and SHINE trials: Interpretation of WASH intervention effects on linear growth and diarrhoea

as a whole, 'product-relevant' R&D is the focus of 41% of total funding by volume; however, funding gaps are apparent, for example, investments in R&D for diagnostics and vaccines are approximately 2/3 lower than for therapeutics. Specifically, human bacterial pathogen R&D focuses mostly on Basic Research (30%) and Therapeutics (28%), followed by Operational research (17%). Vaccines cover 12% of the total investment, while Diagnostics and Capacity Building cover 6% each. It is also noteworthy that 54% of the total investment is defined as "domestic" and 46% as "international funding"; this means that a large portion of funding originates in HICs and remains in HICs.[29]

The AMR R&D Hub has done further analysis to look at the LMIC-relevant specific portion of AMR R&D funding and has found that USD 0.86 billion out of USD 8.9 billion (10%) of total AMR R&D goes to LMIC-specific R&D.[30] Of the USD 0.86 billion, 80% goes to human health, 17% to animal health, 1.6% to plants and 0.6% to environmental AMR R&D. Within the human health category, more than half goes to operational research, 18% to capacity building and 10% to basic research, so there is low activity in LMICs on technology-specific R&D.

Only 5% of AMR R&D funding is directed towards fungal diseases, and of this, 93% goes to human-related research (which is similar to the percentage for the total AMR R&D dataset), 53% goes to basic research (compared to 30% for overall AMR R&D projects) and only 10% goes to operational and implementation research (compared to 20% for the complete dataset). 20% of funding goes to therapeutic R&D and 6% to diagnostics. This shows that on a comparative basis, operational and fungal implementation research is underfunded compared to all AMR R&D investment. Just over three-quarters (79%) of the fungal R&D investment is defined as "domestic", that is, provided to research organisations in the same country where the funder is located. 75% of funding goes toward three fungal infections – Candidiasis, Aspergillosis and Cryptococcosis (caused by *Candida spp*., *Aspergillus spp.* And *Cryptococcus spp.)* – with small percentages going towards Pneumocystis pneumonia, Histoplasmosis , Coccidioidomycosis (caused by *Pneumocystis*, *Histoplasma capsulatum* and *Coccidioides)* and other fungal diseases.[31]

On the regulatory side, the cost and length of clinical trials, relative to the market potential, is problematic.[32] This is linked to increasing recognition of difficulties accessing relevant patients through the traditional Contract Research Organisation (CRO) model. There remain high hurdles for dossier submission to meet requirements of regulators. The challenges relating to dossier submission are exacerbated when it comes to antibiotic alternatives (e.g., phage and microbiome approaches) and, for all technologies, when individual countries require extra, local studies to be done above those required by stringent regulatory authorities to register products in that country. Experts point to the need to improve existing structures that optimise early-stage research, sharing of data and compound libraries, the use of TPP to align research efforts with global needs, and global coordination of early-stage R&D.[33]

According to most interviewees, awareness of the burden of AMR in LMICs is low, linked to the weak (but improving) evidence base referenced in the "Progress" Section 2.1.2. Cultural and individual choices are also an influential part of the enabling environment, as they affect factors such as resistance to vaccination. There is an accepted need for increased education around the importance of AMR.

2.2.2 Progress

The upstream R&D therapeutics space is now relatively well funded, compared to other stages of the R&D pipeline. While some interviewees argued that the upstream funding space is "crowded", considerable scientific challenges continue to complicate early discovery and research for new antibiotics, warranting continued upstream funding.

There has been good progress in building the architecture and potential for coordinating and managing pipelines for technology readiness level (TRL) progression, through Combating Antibiotic-Resistant Bacteria Biopharmaceutical

[29] The Global AMR R&D Hub (2021): Annual Report 2021: The Global AMR R&D Funding Landscape and interviewees with AMR R&D hub team
[30] Defined as: i) Where a HIC funder funds LMIC research organisations directly ii) Where finance from a HIC goes to a HIC research organisation and the subject of the research is directly relevant to LMICs, as judged from reading the abstract or iii) Where an LMIC (Brazil and China included) funds AMR R&D work within their own country
[31] The Global AMR R&D Hub (2021): Public and philanthropic investments in AMR R&D related to fungi
[32] Interviewees
[33] React (2021): Ensuring sustainable access to effective antibiotics for Everyone - Everywhere

Accelerator (CARB-X) Global Accelerator Network, REPAIR-NOVO, Global Antibiotic Research and Development Partnership (GARDP) and now the AMR Action Fund. There has been progress in lowering entry barriers for accessing R&D funding, e.g., through leveraging CARB-X, and a deliberate focus on expanding the involvement of LMIC-based researchers by e.g., BactiVac[34] and the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR).

The enabling environment in **developments in pull incentives** has improved, notably through the UK's subscription-based model of paying for antibiotics[35], although this would only indirectly have an LMIC impact. The Clinton Health Access Initiative (CHAI), GARDP, UNICEF and WHO have been working to solve some of the market-related bottlenecks specific to antibiotic access in LMICs, through the nascent "SECURE" initiative[36]. In diagnostics, there is the Value-Dx initiative, but this is focused on demonstrating the economic value of diagnostics in HICs.[37] Vaccines are in a slightly better position, given there is an established global financing initiative (Gavi, the Vaccine Alliance) to introduce and scale new vaccines, and as the vaccine delivery system is also well established. The Medicines Patent Pool (MPP) is expanding its portfolio beyond AIDS, TB and Malaria and is reported to be exploring licensing opportunities for antibiotics. This might allow practitioners to work on untapped opportunities to address access to existing antibiotics that are still not patented.

On the regulatory side, the Wellcome Trust has been developing an **infectious disease clinical trial network** which aims to improve upon weaknesses of the CRO model, reducing cost and increasing speed of clinical trials. GARDP similarly has been **building capacity for clinical trials** in high-burden LMIC settings through its ongoing trials. In diagnostics, there are precedents to accelerate development and deployment through the WHO Prequalification of Medicines Programme (PQP), but there needs to be greater diagnostic regulatory harmonisation across countries and reform in reimbursement.

AMR awareness at the global level is high, featuring on the agenda of UN[38], G7[39], G20 and World Economic Forum meetings.[40] The research findings from the recent GRAM report in The Lancet[41] should raise awareness of the AMR burden in LMICs specifically. There is an increased recognition of the importance of vaccine R&D due to COVID-19. However, it is not clear how much this boost to vaccine research capacity will carry over into AMR-specific vaccines. There have been structural changes in LMICs for the administration of the COVID-19 vaccine that could be considered/implemented for the roll-out of other vaccines (also for diagnostics). As highlighted in the Wellcome Trust AMR response report[42], more weight is being attached to vaccines in global and national AMR declarations/strategies than five years ago. Additionally, the Immunisation Agenda 2030 frames AMR as one of the key global threats and argues for the need to put additional efforts into vaccine R&D and implementation.

2.2.3 Gaps related to the enabling environment in human health innovation and access

There are some funding opportunities linked to **downstream commercialisation/market shaping** (e.g., nascent SECURE[43]) as well as **therapeutic and diagnostic field validation, commercialisation, and market entry work**. Some interviewees thought that the barriers impeding diagnostic uptake might be overcome by mandating their use e.g., when narrow-spectrum antibiotics are to be used, and/or by covering the costs of their use with public funding, but this requires making an effective economic argument to Ministries of Finance.

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[34] https://www.birmingham.ac.uk/research/immunology-immunotherapy/research/bactivac/index.aspx
[35] See: https://www.bmj.com/content/369/bmj.m2468
[36] https://www.gardp.org/what-we-do/secure/
[37] https://www.value-dx.eu/
[38] Antimicrobial resistance and the United Nations sustainable development cooperation framework: guidance for United Nations country teams (2021)
[39] https://gardp.org/news-resources/summary-g7-leadership-in-accelerating-the-response-to-antimicrobial-resistance-in-the-pandemic-era/
[40] Interviewees
[41] Murray et al. (2019): Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis
[42] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps
[43] Financing mechanisms still being negotiated

There may be opportunities to **increase funding and shift focus of antifungal research**. At present, fungal R&D comprises only 5% of the total AMR R&D funding. In total, 75% of this focuses on three fungal diseases only; downstream fungal R&D is relatively underfunded and most of the funding is going to high-income countries.[44]

The AMR R&D Hub's work has identified that **more technology-related R&D needs to be done in LMICs**, to ensure local relevance and uptake[45], and GAMRIF's ability to fund this type of work is therefore crucial. Work is needed to strengthen **clinical trial network capacity in countries with high AMR**. A widely-supported view from Interviews was that a broader geographic pool of R&D work is needed, especially within LMICs where the AMR burden is high. A broader pool was felt likely to support product development which is better tailored to LMIC healthcare delivery systems and would also enable quicker access to relevant patients. GARDP is developing this capacity but specific to their therapeutic candidate zoliflodacin. The Wellcome Trust's ADVANCE ID initiative[46] has potential to be a systemic clinical trials game changer through reducing the cost and improving speed of R&D but it would be of benefit to industry/private sector, and not just LMICs. In diagnostics, the Feasibility of Novel Diagnostics for TB in Endemic Countries (FEND-TB) clinical trial network for diagnostic R&D is reported to be the closest equivalent but this is in the initial stages of development.

Within the regulatory environment, **regulatory science work could streamline the product development pathway** and some interviewees think that GARDP would be the obvious place to house an initiative addressing this cross-cutting barrier. In diagnostics, there is a **need for regulatory harmonisation to reduce the costs of conducting numerous field trials** and registrations.

In vaccines, **there is a need for more investment into new R&D platforms relevant to AMR** (e.g., DNA and RNA vaccines, novel delivery/administration technologies, modular manufacturing platforms). A need remains to further advocate for the AMR community, despite recognition of immunisation in global AMR strategies, to link the AMR innovation and immunisation agendas with different funders and discussion arenas.

2.3 Human health: Diagnostic innovation and access

2.3.1 Challenges

There are numerous demand and supply-side challenges affecting innovation and access in AMR-relevant diagnostics. On the demand side, the different **use cases are unclear**, namely understanding what products are needed for different syndromes according to the user, purpose, and location of the test within the health system. Diagnostics represent an added expense and demonstrating utility and cost effectiveness is key since diagnostics typically cost more than treatments, and **mechanisms of reimbursement do not incentivise diagnostic use**. Until and unless there is a clear answer as to who to test, when to test and the value of the test, the market size will continue to be unclear, affecting supply-side investment incentives. This is true not only for diagnostics but also for new therapeutics, as increased diagnosis can expand the market opportunity for new therapeutics.

On the supply side, **access is impeded by supplier dominance in existing technologies** (few suppliers, opaque pricing, high costs to switch to new suppliers), high diagnostic prices, as well as regulatory and technological barriers impeding uptake in LMICs. There are supply constraints as well – not only the devices but also access to consumables and maintenance services. According to interviewees, there is a dominance at higher (tertiary) health system levels of diagnostics, with **point of care (POC) devices being less available at community health system levels** and a **lack of suitability of key technologies for frontline use in LMICs.** These constraints result in insufficient use of diagnostics for clinical decision making, inappropriate (over and under) use of antibiotics and lack of surveillance data to understand the baseline AMR

[44] The Global AMR R&D Hub (2021): Public and philanthropic investments in AMR R&D related to fungi
[45] AMR R&D Hub dashboard and interviewees.
[46] ADVANCE ID is jointly funded by the Wellcome Trust and Singapore institutions including the Saw Swee Hock School of Public Health and Yong Loo Lin School of Medicine, National University of Singapore. The vision of the Network is to improve public health by developing the clinical evidence base for the prevention and treatment of drug-resistant infections. Its mission is to build and sustain a strategic clinical research network focused on most efficiently delivering locally relevant interventions for drug-resistant infections.

situation. There also needs to be **better networking of diagnostic data within countries**, to enable surveillance and to gain a better understanding of AMR burden of disease.[47]

2.3.2 Progress

There have been consultations on the demand side, for example through WHO[48], FIND[49] and Unitaid[50], including country focus groups, to try and ascertain how and whether **different types of tests** – especially those which distinguish bacterial versus viral – **might be used in different healthcare settings**.[51] In recent years, there have been major advances in the uptake and use cases for rapid tests for malaria and HIV, seeded by Unitaid and scaled largely with Global Fund Finance, which may provide relevant general lessons for scaling testing. JPIAMR hosted a recent webinar on the lessons learned from the roll-out of the COVID-19 lateral flow POC tests and how this experience might be leveraged for increased use of diagnostic testing with relevance to AMR.[52]

On the supply side, **innovation challenge funds** – Longitude Prize, Horizon Europe - have been fuelling the pipeline, with CARB-X and FIND enabling TRL progression. FIND, Unitaid and the AMR Benchmark are all conducting **technology landscaping** to understand the R&D pipeline and state of technological readiness**.** According to an interviewee, Unitaid's most recent landscaping concluded that the pipeline for a bacterial versus viral test was at too early a stage for its involvement, but there are plans to revisit this conclusion in 2022, with plans being developed to survey STI diagnostic tools. Whole genome sequencing (WGS) prices are reported to be falling rapidly, but equipment and consumables are still priced several times higher in Southeast Asia and Africa than in Europe. The Bill and Melinda Gates Foundation (BMGF) is working with Africa Centres for Disease Control and Prevention (Africa CDC) on a relevant pathogen genomic surveillance project, however some INTERVIEWSs are of the view that WGS remains a non-starter for LMICs at current price points.

There are **64 fungal diagnostic R&D projects captured** in the Global AMR Hub's dataset, with **23 in the development phase and one in the approval and post-approval phase**.[53] According to The Global Action Fund for Fungal Infections (GAFFI), **appropriate diagnostic tests are already** available for many priority fungal infections, and the focus should be on expanding their use through market shaping and implementation science. [54]

2.3.3 Gaps related to diagnostic innovation and access

In 2019, WHO hosted a technical consultation on in vitro diagnostics for AMR. This consultation aimed at identifying gaps in in-vitro diagnostics to combat antibacterial resistance for bacterial pathogens[55] at primary and secondary healthcare facilities (Levels I and II) in LMICs. Consultation feedback is shown in Figure 2.[56] The red cells highlight **the largest gaps in POC syndromic testing relate to diagnostics for sepsis, STIs and pneumonia**. The following R&D priorities were identified, based on the diagnostic gaps identified through consensus views of participants:

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[47] The Lancet (2021). The Lancet Commission on diagnostics: transforming access to diagnostics.
[48] WHO (2019): Technical consultation on in vitro diagnostics for AMR, 27–28 March 2019, WHO Headquarters, Geneva: Meeting report
[49] Several articles on different dignostics and testing technologies at FIND webiste: https://www.finddx.org/
[50] https://unitaid.org/news-blog/unitaid-extends-opp-era-viral-load-initiative/#en
[51] The key conclusions from the Unitaid consultation were as follows: i) Role for biomarker-based tests is to add objective measures to clinical algorithms for acute febrile illness management in LMICs, complementing existing disease diagnostics ii) Low performance of available host-response biomarkers (HRBs) necessitates complex algorithms to support their use and interpretation iii) One-size fits all global guidance on use of HRBs for acute febrile illness management will be difficult to develop and will need to be context-specific. Local epidemiology will influence policy decisions about adopting and using HRBs in particular geographies iv) Broad agreement on the need to improve outcome metrics and study designs to assess biomarker-based tests. Most evidence focuses on comparative performance, rather than the impact of biomarker-based tests on clinical outcomes (source: Unitaid (October 2021): Tools for Childhood Fever Management)
[52] https://www.jpiamr.eu/events/facilitating-amr-research-in-the-covid-19-pandemic/
[53] The Global AMR R&D Hub (2021): Public and philanthropic investments in AMR R&D related to fungi
[54] GAFFI (2017) Delivering on Antimicrobial Resistance Agenda Not Possible without Improving Fungal Diagnostic Capabilities
[55] Included in WHO priority bacterial pathogen list for R&D for drug development (PPL)
[56] WHO (2019): Technical consultation on in vitro diagnostics for AMR, 27–28 March 2019, WHO Headquarters, Geneva: Meeting report

- Simplified phenotypic identification and **Antimicrobial Susceptibility Testing (AST) in key resistance categories,** particularly in blood stream infections e.g., sepsis;
- **Improved diagnostics for AST for Neisseria gonorrhoeae**, in particular i) a rapid test for primary care settings to distinguish between N. gonorrhoeae and chlamydia and ii) a comprehensive test to both confirm N. gonorrhoeae and enable genotypic resistance testing in primary/secondary settings;
- Host response **tests to distinguish between bacterial and non-bacterial infections at primary level,** including further work to nuance the existing TPP;
- **Multiplex platforms to identify bacterial pathogens and perform AST/resistance testing without culture** (for example, from urine, stool, swabs); simple standalone test for AST or resistance testing, minimally to perform testing at primary and secondary level settings without culture.

Figure 2: Priority Gaps in AMR Diagnostics

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

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

If test desired	Available	Not fully available	Not available

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

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

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

(2) In case it is needed in special populations.

(3) Infection marker.

Source: WHO (2019): Technical consultation on in vitro diagnostics for AMR, 27–28 March 2019, WHO Headquarters, Geneva: Meeting report.

The meeting report also showed the need to support **increased access to diagnostic equipment which already exists**. Interviewees said that better diagnostic access is needed in particular for neonatal sepsis – both for hospital as well as POC testing – and making sure that the full antibiotic portfolio is available to respond to any increased diagnosis.

The WHO consultation, as well as experts interviewed, suggested **the need for demand-side work** – including field validation, operational research and commercialisation work – **to look at the value proposition and use cases.**[57] An interviewee had a strong view of the need to better understand the clinical environment in which tests are used, and connect R&D more to the world of policy, civil society, and the enabling environment, in order for technologies to be better prioritised and used.

On the supply side, R&D for new tools is also required. interviews refer to the "holy grail" of a **viral versus bacteria diagnostic test or even bacterial/non-bacterial test.** Ideally, this could be plugged into malaria screening programmes and would need to be supported by improved access to first-line antibiotics. In recent months, interviews report that the

[57] For example, 2 possible use cases for a binary bacterial/non bacterial test could be i) Who: High skilled healthcare workers, Why: To provide an additional data point to inform and give confidence to antibiotic treatment decisions. Where: Hospital out patient departments, Emergency departments, and select primary healthcare centres versus i) Who: Health care workers and minimally skilled primary care providers, but useful for all healthcare workers Why: To determine if a patient would benefit from antibiotics Where: Community and primary level.

Israeli company MeMed has developed the first viral versus bacterial test. MeMed's LMIC commercialisation strategy is yet not clear, and there is scope to conduct field validation of the test in an LMIC setting.

Also on the supply side, FIND's diagnostic for *N. gonorrhoea* still needs regulatory, commercialisation and market entry strategy investment. Field validation work is underway in South Africa and the commercialisation strategy still needs more work, including on manufacturing and the market introduction framing/strategy. Operational research is required to understand how to use GARDP's new gonorrhoea treatment and FIND's gonorrhoea diagnostic in tandem in different health systems. interviews report that the global AMR community is looking to the zoliflodacin/FIND diagnostic as a test case/pathfinder for new antibiotic and diagnostic co-introduction.[58] Investment is needed into a parallel market entry piece of work to support work in this area. Interviews mention that STI detection would be better supported by a diagnostic which could test, not just for gonorrhoea, but also for syphilis and chlamydia. The development of such a comprehensive diagnostic test would ideally be supported by complementary work on Benzylpenicillin access.

Experts also voiced that diagnostic R&D pipeline management needs to be a leaner and more strategic approach. It seems there are multiple projects underway around the world for a gonorrhoea diagnostic, with no comparative work to understand which will integrate best in LMIC health systems and meet the TPPs. A better overview of R&D activity and pipeline products is needed and Unitaid is planning some work in this area. There also needs to be improved coordination between diagnostic and therapeutic R&D, supporting co-introduction.

As was mentioned in Section 2.2.3, interviewees felt that a clinical trial network for diagnostics is needed in the architecture for managing diagnostic R&D. A network of sites with good capacity would enable evaluation work to start quickly. Interviews felt that FEND/European and Developing Countries Clinical Trials Partnership (EDCTP) would offer the best potential for building this capacity.

Other "niche" areas noted by Interviews for potential GAMRIF investment include:

- Building on previous demonstration work in Africa and Latin America, GAFFI would like to increase the funds going into LMICs to conduct operational research to introduce and scale fungal-relevant diagnostics that already exist. Unitaid is doing market shaping for HIV–associated cryptococcal meningitis but there is no work for histoplasmosis, aspergillosis, or fungal keratitis and limited work for chronic skin problems like mycetoma. According to GAFFI, two priority R&D areas would be: i) Histoplasmosis in AIDS, often combined with TB so azoles cannot be used due to drug interactions; the diagnostic is an easy-to-use urine-based antigen test and the therapeutic is available. Implementation research is needed to diagnose and treat patients who are very ill, so survival benefit could be easily demonstrated. ii) Aspergillosis, with no diagnostics currently available, yet it remains highly under-diagnosed and implementation science is needed to design effective relevant fungal diagnostic tools.
- There are numerous artificial intelligence solutions to aid in diagnostic interpretation as well as clinical decision-making. However, the latter is complicated by the need to adapt the diagnostic tools to cater for the nuances of each health system. There are also many clinical decisions support tools available and in late-stage development, which makes it challenging to capture them all in a landscaping analysis, although FIND has been working on this.
- Better-connected diagnostic platforms and databases are required, to enable data sharing and pandemic response preparedness.
- Interviewees report that there is a rapid low-cost kit to detect falsified medicines in late-stage development at the University of Notre Dame (US). This might address the need for increased identification of falsified medicines, and support research to look for correlation with AMR patterns. Such a project might be supported by a delivery partner running a request for proposals, selecting the candidate with the product profile and commercialisation potential best matching LMIC needs.

Consistent with the challenges and gaps identified in this section of the report, the diagnostics portion of the GAMRIF gap analysis survey offered the seven shortlisted intervention areas and asked respondents to indicate their relative

[58] Interviewees also note that industry is resistant to the concept of co-introduction as a norm, as they perceive it as raising entry barriers for antibiotics R&D and are of the view that co-introduction should not become a regulatory requirement for new antibiotics market introduction and use.

importance. The table below shows how respondents rated the shortlisted diagnostics priority intervention areas using a scale between one and five[59]. All areas had high percentage of five's "critical priority", which lends credence to our shortlisting of priority gaps. The consensus top priority is "Research utility/use case/potential role of diagnostics within the healthcare delivery system in LMICs" while opinion was most divided on "Adapt/repurpose or negotiate tiered pricing for existing diagnostic tools". Regarding the latter, 22% respondents did not know/prefer not to say.

Table 1: Diagnostics priority intervention areas (survey)

Diagnostics	Don't know/prefer not to say	1. Not a priority	2. Minor/low priority	3. Medium priority	4. High priority	5. Very high/critical priority
Continue to build the evidence base on the burden of AMR (for specific pathogens at regional and national level) to inform prioritisation of diagnostic tool R&D	2%	2%	7%	19%	37%	33%
Research utility/use case/potential role of diagnostics within the health care delivery system in LMICs	9%	0%	6%	13%	30%	43%
Streamline/ harmonise regulatory and registration processes for new diagnostics	11%	0%	9%	26%	30%	24%
Adapt/repurpose or negotiate tiered pricing for existing diagnostic tools	22%	4%	7%	26%	17%	24%
Build diagnostic clinical trial network capacity in countries with high AMR burden to reduce the cost and increase the speed of new diagnostic registrations	7%	0%	0%	9%	39%	44%
R&D for new LMIC-relevant diagnostic technologies to improve the existing pipeline	4%	0%	2%	17%	35%	43%
Better coordination of R&D activities between diagnostics and therapeutics, towards co-introduction	7%	0%	6%	17%	39%	31%

Source: GAMRIF gap analysis survey

[59] 1. Not a priority, 2. Minor/low priority, 3. Medium priority, 4. High priority and 5. Very high/critical priority.

2.4 Human health: Therapeutic innovation and access

2.4.1 Challenges

The public health problem with regard to therapeutics has been well documented[60,61,62]: AMR is a growing problem globally, with LMICs disproportionately affected; common diseases (urinary tract infection (UTIs), respiratory tract infection (RTIs) and sexually transmitted infections (STIs)) are becoming untreatable; and the **rate of spread of resistance outweighs the pace of new drug development.** According to interviewees and reviewed literature, the relatively slow-pace of new drug development is linked to well-known difficulties related to the exit of several big pharmaceutical players from antibiotic R&D, economic and capacity challenges faced by small and medium sized enterprises (SMEs) and biotechnology companies, and therefore the need to generate a pipeline of novel therapeutics[63,64,65]. Innovative activity suffers from high R&D cost and regulatory hurdles in comparison with the market potential. The 2019 clinical pipeline analysis by the WHO[66] showed that **32 of the 60 candidates in clinical development target the WHO priority pathogens** and only two out of 32 target high-priority MDR bacteria. **Pathogens that have a serious health impact in LMICs,** such as *S. typhi* and *A. baumannii*, have hardly any promising drug candidates in the pipeline.

There are **important access challenges to existing therapeutics** including:

- High prices of newer antibiotics, e.g., a course of second- or third-line antibiotics costs a year's wages in India.
- Few paediatric antibiotic formulations.
- Poor access to existing first-line antibiotics, partly due to price pressure and manufacturer exit. For example, there is a lack of availability of antibiotics used to treat paediatric community-acquired pneumonia (CAP), even though there is dispersible amoxicillin on the market.

This lack of access results in the wrong antibiotics being used. Moreover, the lack of access to existing therapeutics enhances the conditions for antibiotic resistance. There is also insufficient access to first-line antifungals and an increasing burden of antifungal resistance, alongside toxicity and drug interaction issues, especially for patients on TB medications. Finally, there are limited market-shaping initiatives to work on improving access in LMICs and commercialisation strategies.

2.4.2 Progress

There has been progress in therapeutic innovation, R&D pipeline funding and TRL advancements, notably through the activity of CARB-X, GARDP, NOVO-REPAIR grants and fellowships. The AMR Action Fund, which initiated in December 2020, brings potential to the field as well.

The WHO 2020 pipeline analysis[67] showed a clinical antibacterial pipeline focused on the PPL and **increased innovation but with some remaining gaps**. Of 43 antibiotics and combinations with a new therapeutic entity and 27 non-traditional antibacterial agents, 26 are active against the WHO priority pathogens, 12 against *Mycobacterium tuberculosis* and five

[60] 2020 Antibacterial Agents in clinical and Preclinical Development: An overview and analysis. Geneva: World Health Organization; April 2021
[61] WHO criteria for therapeutic innovativeness (new class, new molecular target, new mode of action, no cross-resistance with existing drug classes).
[62] Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021
[63] 2020 Antibacterial Agents in clinical and Preclinical Development: An overview and analysis. Geneva: World Health Organization; April 2021
[64] WHO criteria for therapeutic innovativeness (new class, new molecular target, new mode of action, no cross-resistance with existing drug classes).
[65] Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021
[66] WHO (2020): 2019 antibacterial agents in clinical development: An analysis of the antibacterial clinical development pipeline
[67] 2020 Antibacterial Agents in clinical and Preclinical Development: An overview and analysis. Geneva: World Health Organization; April 2021

against *Clostridium difficile*. Of the 26 antibiotics active against the WHO priority pathogens, seven fulfil at least one of the WHO innovation criteria[68], but only two of these are active against the critical MDR Gram-negative bacteria.

Similarly, the 2021 AMR Benchmark[69] published recently (with different inclusion cohort versus the WHO analysis[70] as it included antifungal R&D) found progress in the R&D pipeline. Among the eight large research-based companies included in the survey, **92 R&D projects targeted infections caused by WHO priority pathogens (namely the bacteria and fungi posing the highest risk to human health** due to drug resistance). This is a **modest increase from 2020**, when the same eight companies were developing a combined 77 projects. However, the pipeline remains small relative to the scale of the AMR threat.

The R&D pipeline has also diversified, with more funding to antibiotic alternatives and preventatives, including through GAMRIF and the BMGF support to CARB-X. The WHO 2020 pipeline analysis showed that 27 non-traditional antibacterials are in the pipeline: nine antibodies, four bacteriophages and phage-derived enzymes, eight microbiome-modulating agents, two immunomodulating agents and four miscellaneous agents.

CARB-X's accelerator programme has expanded its reach and is **filling SME capacity gaps**. There has been important progress on development of access and stewardship plans, which help support access to and stewardship of future products. The 2021 AMR Benchmark report found that 18 out of 20 late-stage medicine R&D projects in the analysis have both access and stewardship plans in place. This is an area of sustained progress since the first Benchmark report was published. Access and stewardship plans are expanding and becoming more detailed which may be a sign of improved quality.[71]

Entasis zoliflodacin (licenced by GARDP) for ***N. gonorrhoeae* is progressing well through clinical trials,** and with plans for a complementary *N. gonorrhoeae* diagnostic, being developed by FIND, to be ready in time for co-introduction.

There are **13 therapeutic R&D fungal projects, five of which are in the development phase**. A WHO priority list for antifungals has been developed, but it is not yet published. According to interviewees, there are **four antifungal projects in the R&D pipeline** being developed against fungal pathogens in scope (*Candida* spp. and *A. fumigatus*). All are in discovery stage, except Fosmanogepix, a potential first-in-class antifungal in Phase II development by Pfizer.[72] The FDA has issued a priority voucher for work on a cryptococcal meningitis therapeutic and Drugs for Neglected Diseases initiative (DNDi) is working on fosravuconazole, a therapeutic to help people suffering from moderate eumycetoma, the fungal form of mycetoma[73].

There have also been developments to support **increased access to existing antibiotics**. GARDP, Shionogi, and CHAI are working together on a project to reformulate the antibiotic cefiderocol for paediatric use. CHAI and GARDP with UNICEF and WHO are working on the SECURE initiative (see Section 2.4.2) and the Medicines Patent Pool's expanded strategy includes AMR, but so far MPP has only secured voluntary licenses for TB drugs. Despite these developments, the 2021 AMR Benchmark concluded that there is a lack of momentum in providing access to existing antibiotics and other antimicrobial products in LMICs.

2.4.3 Gaps related to therapeutic innovation and access

Most of the R&D projects that address Gram-negative bacteria target the most critical and urgent threats.[74] The projects targeting these pathogens include two recently approved medicines: relebactam/imipenem/cilastatin from Merck Sharpe

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[68] WHO criteria for therapeutic innovativeness (new class, new molecular target, new mode of action, no cross-resistance with existing drug classes).
[69] Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021
[70] WHO (2021): Comprehensive Review of the WHO Global Action Plan on Antimicrobial Resistance
[71] Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021
[72] WHO (2021): Comprehensive Review of the WHO Global Action Plan on Antimicrobial Resistance
[73] https://dndi.org/research-development/portfolio/fosravuconazole/#:~:text=DNDi%20is%20currently%20preparing%20for,with%20the%20current%20treatment%2C%20itraconazole.
[74] These pathogens are: Enterobacteriaceae (including carbapenem-resistant *Enterobacteriaceae*, or CRE, and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae), *P. aeruginosa* (including carbapenem-resistant and multidrug resistant *P. aeruginosa*) and carbapenem-resistant *Acinetobacter* spp.

& Dohme, and cefiderocol from Shionogi. The remaining priority Gram-negative pathogens are targeted by just a handful of projects. This includes some discovery/preclinical projects targeting *Salmonella* spp. and *Shigella* spp. There are no products in the pipeline for some priority Gram-negative pathogens: *Campylobacter* spp., *Helicobacter pylori* (both categorised as high priorities by WHO) and *Mycoplasma genitalium* (on the watch list of the CDC).[75] Some experts argue that there are enough financing initiatives which target early-stage research. However, fundamental scientific challenges for antibacterials are still largely unresolved, e.g., getting compounds into hard-to-permeate Gram-negative bacteria and understanding the circumstances under which clinically relevant resistance mutations arise. One interviewee suggested that the use of Artificial Intelligence (AI) in drug discovery could be applied to some of these scientific challenges.

GAMRIF has been funding antibiotic alternatives (e.g., phages, probiotics), however these have a problematic use case due to the variable efficacy that prevents these therapeutic products to enter some markets which have challenging regulatory pathways.

As with diagnostics, there is a need for use case/work to shape the demand side for antibiotic alternatives as preventatives. Since antibiotic alternatives could be used preventatively, although not uniquely, they may suffer similar economic challenges as diagnostics in that they would cost extra. One interviewee said that these innovations are consequently more likely to be used in high-income settings versus LMICs.

There remains a significant barrier for LMICs to access existing treatments due to high pricing, lack of supply, few paediatric formulations and limited market shaping work to address these challenges. The AMR Benchmark[76] concluded that pharmaceutical companies are not taking the necessary steps to provide access to the antibiotics and antifungals in their portfolios in LMICs. Additionally, where access strategies are in place, they remain focused on a small set of countries, people, and diseases. Many interviewees for this analysis said that there are untapped opportunities for market shaping to address access to existing antibiotics, including work to develop paediatric indications, antibiotic reformulation work to reduce cost or improve shelf life, and increased use of tiered pricing as part of access strategies. Securing voluntary licensing agreements to expand production capacity and increase competition would be valuable for newer antibiotics, while procurement approaches as envisaged through the SECURE initiative may enable LMICs to secure better pricing and steady antibiotic supply. According to a few Interviews, "SECURE is the best opportunity on the table right now, but it's not fully baked yet. It needs more work to become a testable proposition."

Work is needed to develop the use case and shape the market for product introduction for late-stage innovations. It would be sensible to focus market shaping work on the products which are closest to market, those being therapeutics for i) sepsis and neonatal sepsis ii) gonorrhoea/STIs. Entasis' zoliflodacin is high priced compared to standard therapy, so there is a need for further work to lower the price. Market entry analysis is also needed, to help understand the trigger points to bring zoliflodacin from a second line to a more accessible choice of therapy. This requires operational research to know how to use zoliflodacin in different healthcare system settings. Market entry work needs to bring together surveillance data and ensure the price is affordable.

Gaps in antifungal therapeutic innovation and access might be met through i) expanding the scope of GARDP, DNDi and/or CARB-X ii) and/or funding implementation research through GAFFI. Interviewees felt that the best focus in antifungals would be market shaping and operational research to expand diagnosis and match with antifungal availability.

As in the challenges and gaps identified in this section of the report, the therapeutics portion of the GAMRIF gap analysis survey proposed eight shortlisted intervention areas and asked respondents to indicate their relative priority. The table below shows how the respondents rated the shortlisted therapeutic priority intervention areas using a scale between one and five[77]. Seven out of the eight intervention areas were rated as high priority or very critical priority, which lends credence to our shortlisting of priority gaps. Survey respondents indicated the lowest priority for "Invest in operational research to better understand the use case for zoliflodacin in different health systems" and "Antifungal R&D"; these areas might have been seen as lower priority because fewer people were aware of the challenges in these relatively more specific and niche areas.

[75] Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021
[76] https://accesstomedicinefoundation.org/amr-benchmark
[77] 1. Not a priority,2. Minor/low priority, 3. Medium priority, 4. High priority and 5. Very high/critical priority.

Table 2: Therapeutics priority intervention areas (survey)

Therapeutics	Don't know/prefer not to say	1. Not a priority	2. Minor/low priority	3. Medium priority	4. High priority	5. Very high/critical priority
Continue to build the evidence base on the burden of AMR (for specific pathogens and at regional and national level) to inform prioritisation of therapeutic R&D	4%	2%	6%	20%	37%	31%
Invest in R&D for therapeutics that are in late-stage R&D - e.g., antibiotics for gonorrhoea	6%	0%	4%	17%	44%	30%
Invest in operational research to better understand the use case for Zoliflodacin in different health systems	33%	2%	9%	24%	22%	9%
Anti-fungal R&D	17%	2%	4%	26%	35%	17%
Invest in late-stage R&D and/or market shaping to address access to existing antibiotics e.g., Paed indications, reformulation, voluntary licensing, demand side/use case research, price negotiatio...	7%	0%	6%	15%	39%	33%
Invest in regulatory science-research, to increase speed and reduce costs of regulatory approval for therapeutics	7%	0%	11%	22%	35%	24%
Build therapeutic clinical trial network capacity in countries with high AMR burden needs, in order to reduce the cost and increase the speed of registration costs of new therapeutic registrations	6%	0%	2%	13%	46%	33%
Invest in R&D of therapeutic alternatives such as phages and probiotics	9%	0%	6%	24%	30%	31%

Source: GAMRIF gap analysis survey

2.5 Human health: Vaccine innovation and access

2.5.1 Challenges

There are several challenges that hinder the development of and access to vaccines globally, but particularly so in LMICs. One of the main challenges is the **low uptake of existing vaccines** (e.g., Pneumococcal Conjugate Vaccine at uptake of 40%).[78] Significant progress has been made, but LMICs still struggle to provide and improve access to the most basic vaccinations due to their poor overall health systems, insufficient supply chains and inadequate data collection management systems which have led to stock-outs.

However, there are more positive developments in access to vaccines in LMICs relative to access to therapeutics and diagnostics. For example, 72% of on-patent vaccines are supported by at least one access strategy compared to other products with rates under 30%.[79] This high rate might likely be reflecting the role of supranational procurement mechanisms such as Gavi - The Vaccine Alliance. Moreover, several companies are working towards improving access to antibacterial vaccines through tiered pricing policies and public or private partnerships.[80]

On the R&D side, challenges that are **hindering the development of vaccines for AMR** include:

- **The technological complexity.** Emerging bacterial and fungal pathogens have complex resistance profiles which make it difficult to quickly develop effective vaccines. Pathogens like *K. pneumoniae* have diverse, variable, and complex structures for which it is difficult to find antibodies that would protect against them.
- **The limited consideration of how future vaccines might impact on AMR when carrying out cost-effectiveness analyses.** According to the reviewed literature, more sophisticated methods to measure cost-effectiveness of vaccines should be implemented. Measures are needed to quantify the microeconomic (i.e., individual- and household-level) consequences of vaccination as opposed to no vaccination for people's health (including AMR infections) and socio-economic situation. The variables to consider include: "out-of-pocket health and care-related expenditures, caregiving time, education, paid and unpaid productive work, consumption of goods and services, leisure, exposure to financial risk, and income and wealth". [81]
- **The balance between developing new vaccines versus increasing the reach or/and repurposing existing ones**. Interviews have mixed views whether to invest in innovative R&D, adaptive R&D, or both for vaccine development. Some believe that more emphasis should be given to repurposing some existing vaccines, for example the meningitis vaccine which has been shown to have some protective effect against gonorrhoea. Others mentioned that more investment into innovative R&D should be the focus as there are still many pathogens with no products in the pipeline e.g., *Campylobacter* spp., *H. pylori* (both categorised as high priorities by WHO) and *M. genitalium* (on the watch list of the CDC). [82]

2.5.2 Progress

Despite some of the challenges mentioned in the previous section, **there has been substantial progress in three areas related to vaccine innovation and access:** the availability of existing vaccines against pathogens included on the WHO priority list of pathogens – particularly for Pneumococcal Conjugate Vaccine and influenza; the use of novel technologies and approaches for current and future vaccine R&D, including technologies to administer vaccines; and the development of new vaccines against pathogens in the WHO priority list.

According to interviewees, **the roll-out of the Pneumococcal Conjugate Vaccine and influenza vaccines has improved in the last years**. For example, India has recently announced the completed roll-out of Pneumococcal Conjugate Vaccine in all states, and other countries, such as Bangladesh and China, are working towards the roll-out of the Pneumococcal Conjugate Vaccine with support from international funders. In addition to the increased availability of these vaccines, **the impact on AMR of these vaccines** together with *S. typhi* **is well documented.** Many studies indicate a significant decrease in the prevalence of antibiotic-resistant pneumococcal disease after the introduction of the Pneumococcal Conjugate

[78] Wellcome and Boston Consulting Group (2018): Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities
[79] Ibid
[80] GSK is working together with Médecins Sans Frontières and UNICEF.
[81] Micoli, F., et al. (2021): The role of vaccines in combatting antimicrobial resistance
[82] Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021

Vaccine.[83] Moreover, multiple studies have noted indirect effects even of influenza vaccination on AMR, with antibiotic prescriptions decreasing by 13 to 50 % among those vaccinated compared to unvaccinated control groups. Some interviewees highlighted the learnt lessons of the roll-out of the COVID 19 vaccine in LMICs should be considered for the role out of vaccines against WHO priority list of pathogens.

Furthermore, interviewees mentioned that **progress has been made in the use of novel technologies and approaches for the development of new vaccines and their administration**. Some of the novel technologies being used to develop new vaccines include: i) reverse vaccinology, ii) the use of novel adjuvants, iii) structural vaccinology and iv) bioconjugates and bacterial outer membrane vesicles (OMVs). Moreover, there has been progress in polysaccharide conjugation (linking of a bacterial polysaccharide to a carrier protein) and antigen design which are also promising for the future of vaccine research and development. OMV technology is being used to develop *N. gonorrhoeae* vaccines[84] and the technology also proved successful in developing a vaccine for *Neisseria meningitidis* in 2005. Other OMV-based vaccines for many pathogens are at the preclinical stage. Innovative synthetic and bioconjugation strategies are substituting traditional conjugation approaches and are more advanced in terms of clinical development (for example, for *Shigella* species or *E. coli*).[85] According to interviews, the use of new adjuvants may increase vaccine efficacy, particularly of protein-based vaccines. Older technologies, such as live attenuated and inactivated vaccines remain good alternatives due to their simplicity and low cost of manufacture. Additionally, more conventional approaches can be enhanced – for example the design of safer live attenuated vaccines, simplifying processes for polysaccharide purification, and improving production of glycoconjugates.[86] The development of **new ways to administer and deliver vaccines has also improved over the last years** – particularly through the work of the Vaccine Innovation Prioritisation Strategy (VIPS) group.[87] The VIPS project started in 2018 with the ambition to fund vaccines innovation to improve the reach and uptake of vaccines in LMICs. According to Interviews, the VIPS project is working on three vaccine administration, delivery, and control technologies: Micro-Array Patches (MAPs) to release the vaccine through the dermis[88], barcodes to enable improved supply chain management[89], and controlled temperature change monitors.[90]

Annex 7 provides **an overview of the current vaccine development pipeline, feasibility for vaccine development and possible interventions for key pathogens included in WHO priority list of pathogens** that pose the greatest threat to human health. Several highlights in the development of vaccines are particularly impactful for LMIC contexts:

1. **The pipeline for a Shigella vaccine includes a moderate number of candidates.** Experts believe that a vaccine against Shigella will be successfully developed and marketed; however, given the length of time that development takes, it will likely be five years before a vaccine is licensed. A vaccine against Shigella would represent a breakthrough due to high incidence and significant associated mortality, particularly in LMICs.
2. **According to Interviews, the *N. gonorrhoeae* vaccine is due to reach the market in 2023 or 2024**. The case for development of a vaccine targeting *N. gonorrhoeae* has been strong due to high incidence, high morbidity, and circulation of resistant strains.
3. **There is a candidate vaccine for *E. coli*.** High antigenic diversity of *E. coli* is a challenge for vaccine development, but the inclusion of LT toxoid and fimbria antigens in a potential vaccine may help cover 70-80% of strains.
4. **A non-typhoidal *Salmonella* vaccine** appears technically promising and impactful in LMICs given high disease burden in Africa.

[83] Vaccines to tackle drug resistant infections – an evaluation of R&D opportunities, Wellcome Trust and BCG (2019)
[84] Ibid
[85] Ibid
[86] Ibid.
[87] Kristensen, D., et al. (2021): A global collaboration to advance vaccine product innovations – The Vaccine Innovation Prioritisation Strategy
[88] Patches that are applied to the skin and release the vaccine through the dermis. The current MAPs prototypes are used for single dose vaccines. This type of vaccine administration has several benefits: due to its dry format it is easy to store, it is easy to administer and does not require qualified personnel to be administered. Current trials are being carried out for Measles and Rubella. Moreover, Interviews highlighted that the next step will be to use this technology for *Pseudomonas aeruginosa* and Enterobacteriaceae.
[89] Barcodes for quick delivery and standardisation. It is a "system technology that would strengthen accuracy and efficiency in tracking vaccine products to reduce vaccine stockouts and wastage and strengthen accuracy and efficiency in patient vaccination records to monitor coverage and track adverse events".
[90] Monitors show that if a vaccine has been taken out of its cold chain for a certain number of days it is no longer usable.

5. **Several private companies are supporting the local development of a new Pneumococcal Conjugate Vaccine (Prevnar13®) in South Africa,** from raw materials to fully released and packaged products.

Finally, according to interviews, there is only one fungal vaccine project in development phase (Vesivax) for *Aspergillus fumigatus*. Given the likely high cost once marketed, experts highlighted that this is not the highest priority for near-term LMIC AMR impact.

2.5.3 Gaps related to vaccine innovation and access

There are several ways to potentially improve the development and access of vaccines in LMICs. Firstly, according to Interviews, there is a **need to invest further in operational research to increase the uptake of existing vaccines**. Survey respondents also considered this area to be a very critical/high priority (80% of 49 respondents). As mentioned in Section 2.5.1, there are several operational challenges that are hindering the uptake of existing vaccines and some of these challenges could be addressed through more targeted research.

Another priority is **the investment in early-stage research for high-impact pathogens with unclear R&D feasibility** including *Pseudomonas aeruginosa*, *S. aureus* and *E. coli*.[91][92] Moreover, there are pathogens (see Annex 7) – such as *Campylobacter spp*. and *H. pylori* – for which there are no products in the pipeline and further research in this area should be considered. According to the new GRAM report in the Lancet, "vaccines are available for only one of the six leading pathogens (*S. pneumoniae*), although new vaccine programmes are underway for *S. aureus*, *E. coli* and others".[93]

There is a need to invest in studies that look at other pathogens for which **the value of vaccine development is unclear,** e.g., *K. pneumoniae* and *P. aeruginosa*, rather than other products and/or interventions. It would be important to research aspects such as the feasibility of vaccine development and implementation, and the likelihood of introduction in hospital settings (for example, after surgery).

There is a need to better understand **the proportion of burden of disease that can be reduced by a single intervention or a combination of interventions**. The Organisation for Economic Cooperation and Development (OECD) has worked on comparing the impact of different interventions on AMR, for example WASH programmes and multi-thematic programmes, and in their latest work they have included vaccines. The OECD research only includes OECD countries; a similar approach would be particularly useful for LMICs.

Several interviews mentioned how important it is to consider **the repurposing of existing vaccines**. Some work has been undertaken to find out the potential of an mRNA vaccine for AMR; including an initiative to co-administer glycoconjugates and mRNA vaccines which might play a significant role in LMICs.

More support for academic groups working on modelling is needed, particularly in terms of working on investigating the potential of mRNA vaccines and how these can make a difference for AMR, and further research to repurpose other existing vaccines. Adjuvants might also play an important part in the repurposing of vaccines and future vaccine development, as adjuvants have the potential to reanimate and boost older successful vaccines to increase their effectiveness. One interviewee stated that "adjuvants are very important and have a very relevant place in improving vaccines and directing vaccines. It is probably a priority also for LMICs as there are still diseases that we have not conquered, and adjuvants are one of the tools we need to see if we can do better". A few laboratories in Africa are researching the use of adjuvants in vaccines and highlighted that more research and support will be needed in this area.

Other gaps related to vaccine innovation and development identified include:

- **Focus on increasing access through further supply availability.** Despite some progress in new and easy to use technologies and approaches to administer and deliver vaccines, further resources need to be focused on the commercialisation and uptake of these technologies – e.g., through technology transfer programmes. For example, needle-free jabs are being used in India, but these are not yet used widely due to the limited domestic production. This technology has the potential to overcome some cultural barriers, fear of needles, and potential to be administered by a wider cadre of healthcare professionals.
- **Data collection activities and research to explore preventive alternatives for pathogens less well-suited to vaccine development** including *Acinetobacter baumannii*, *Campylobacter*, *Enterococcus faecium*, Enterobacteriaceae,

[91] Vaccines to tackle drug resistant infections – an evaluation of R&D opportunities, Wellcome Trust and BCG (2019).
[92] E.coli causing UTIs
[93] Antimicrobial Resistance Collaborators (2022): Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis

Helicobacter pylori, *Klebsiella pneumoniae* and *Salmonella* paratyphi.[94] Interviews highlighted that there is a lack of activity in this space and that it is important to investigate alternatives such as monoclonal antibodies. Some companies are investigating and researching the use of monoclonal antibodies to combat infections arising from pathogens with highly complex resistance structures.

- **Developing vaccines that target all (or almost all) hospital-acquired infections as well as the viable combination of vaccines**. According to one interviewee, the AMR community could investigate developing multiantigen vaccines like Hexavalent[95] that protects again six different antigens, for example an anti-diarrhoea vaccine that is protective against *E. Coli*, Shigella, Rotavirus and Norovirus.

Consistent with the challenges and gaps identified in this section of the report, the vaccine portion of the GAMRIF gap analysis survey offered the six shortlisted intervention areas and asked respondents to indicate their relative importance. The table below shows how the respondents rated the shortlisted vaccines priority intervention areas using a scale between one and five[96]. "Operational research aimed at increasing uptake of existing vaccines in LMICs" and "early-stage research for potentially high-impact vaccines" were considered the most critical priorities while the other four areas (adjuvant formulation research, research into new methods to administer vaccines, improve evidence base on the linkages between human and animal health and research to develop more sophisticated methods to quantify AMR benefits of immunisation) were also considered of high priority but not as critical. The responses in the open text portion of the survey are consistent (albeit with more detailed examples) with the gaps identified in this Section of the report.

Table 3: Vaccines priority intervention areas (survey)

Vaccines	Don't know/prefer not to say	1. Not a priority	2. Minor/low priority	3. Medium priority	4. High priority	5. Very high/critical priority
Operational research aimed at increasing uptake of existing vaccines (e.g., PCV vaccine) in LMICs	8%	0%	2%	8%	45%	37%
Early-stage research for potentially high-impact vaccines	2%	0%	4%	14%	39%	41%
Adjuvant formulation research (adjuvants potential to reanimate and boost older/less successful vaccines while boosting immune system	10%	0%	8%	33%	37%	12%
Research into new methods to administer vaccines	10%	2%	6%	22%	33%	27%
Improve evidence base on the linkages between human and animal health to ensure learning from human vaccine development and vice versa	8%	0%	10%	24%	39%	18%
Research to develop more sophisticated methods to quantify AMR benefits of immunisation	8%	0%	14%	20%	37%	20%

Source: GAMRIF gap analysis survey

[94] Ibid.
[95] The 6-in-1 vaccine gives protection against these six serious diseases: diphtheria, tetanus, whooping cough (pertussis), polio, Hib disease (Haemophilus influenzae type b) and hepatitis B.
[96] 1. Not a priority,2. Minor/low priority, 3. Medium priority, 4. High priority and 5. Very high/critical priority.

2.6 Plant, environment and animal health: Evidence-informed decision making

2.6.1 Challenges

Although **AMR in the environment** can occur by natural selection at low levels, research shows that high concentrations of Antibiotic-Resistant Bacteria (ARB) and antibiotic resistance genes (ARGs) are caused by human activities[97] - e.g., waste from humans and animals, pharmaceutical manufacturing waste, and use of antimicrobial pesticides for crops.[98]

A **transmission pathway** through the environment is now widely accepted, although the evidence is circumstantial. It is thought that environmental systems can contribute to AMR in three central ways: i) as a transmission pathway, ii) as a reservoir of novel genes, and iii) as a selective pressure for the development of resistance through complex mixtures of pollutants. However, there is uncertainty around the **ecological factors** which might contribute to the development and spread of AMR in the environment, the levels of antibiotics in the environment that are safe/unsafe, the scale of the problem and, most importantly, the effects of environmental contamination on **human health**. This links to the scientific difficulty in analysing complex and interconnected environmental systems, for example showing clear cause and effect on human health[99]. High concentrations of antimicrobials in discharges due to Active Pharmaceutical Ingredient (API) manufacturing[100] have been recorded. However, determining "safe" or "acceptable" levels of discharges is challenging and depends on whether the goal is to protect human health, the environment, or both. [101] [102]

LMICs are likely to be disproportionately affected by environmental contamination due to **poor sanitation systems** and **suboptimal wastewater management**. This is exacerbated when other environmental issues are also prevalent, such as places with significant air pollution, where linked respiratory conditions might be wrongly treated with antibiotics. Among LMICs, the WHO Southeast Asia countries pose the highest risk of emergence and spread of AMR among all WHO regions, as they face these challenges and are home to some of the world's most densely populated cities, with these cities potentially serving as reservoirs for drug-resistant pathogens.[103]

LMICs also face significant **challenges in estimating deaths caused by drug-resistant infections** as there is limited surveillance and laboratory infrastructure to monitor and record this information. Plus, drug-resistant infections are also not always captured in death registers. This is a broader challenge of AMR, which becomes increasingly more complicated when attempting to trace back to complex environmental systems as the initial cause of infection.

Antimicrobials are commonly used as pesticides in plants to manage crop disease. Diseases can be extremely damaging to the income of farms and cause disruptions to the food supply if not treated.[104] **Overuse of antimicrobials in plants**, as well as misuse can lead to the development and spread of AMR, for example using antibiotics to treat or prevent fungal infections, instead of targeted antifungals or disease prevention strategies. AMR in plants can mainly develop and spread through food (through human/animal consumption) and waste (farm run-offs).

The main challenge of AMR in plants, according to existing literature and our interviews, is the **"lack of data to support even an initial scoping of the problem"**.[105] High concentrations of antimicrobials are applied to the environment, for example through mass crop spraying in farms. However, the lack of evidence on this issue means **we do not understand the scale of this use nor the potential consequences for human health.** This becomes increasingly more challenging for LMICs, as the data available on use and health consequences is even more limited.[106] There is a **significant lack in many countries of the surveillance programmes** required to produce evidence. Where in-depth studies have been conducted,

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[97] Branchesme, F. & Munir, M. (2018): Strategies to Combat Antibiotic Resistance in the Wastewater Treatment Plants
[98] Wellcome (2018): Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges
[99] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps
[100] Larsson, D., G., J. (2014): Pollution from drug manufacturing: Review and perspectives.
[101] Wellcome (2018): Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges
[102] Larsson, D., G., J. (2014): Pollution from drug manufacturing: Review and perspectives
[103] Lo Yan Yam, E., et. al (2018): Antimicrobial Resistance in the Asia Pacific region: A meeting report
[104] Wellcome (2018): Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges
[105] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps
[106] Ibid

the results have been sobering. A study in Costa Rica found that the amounts of tetracycline and gentamicin used in on crops were 200–700 times the quantities used in human medicine.[107]

A recent study also showed that **"antibiotics are being recommended far more frequently and on a much greater variety of crops than previously thought",**[108] with the recommendations varying widely between and within LMICs. The study highlighted that agricultural advisors in LMICs are still recommending antibiotic use on crops, while sometimes antibiotics are wrongly recommended to treat fungal infections or as preventative insecticides.

Although antimicrobial use data in **animals** is sparse in most LMICs, it is recognised that livestock accounts for the majority of global antibiotic consumption, up to as much as 80%.[109] The relevance of this for human health is the evidence showing a relationship between antibiotics used in animals reared for food and those to which humans have developed resistance over the past 20 years.[110] **Clear linkages of AMR transmission from animals to plants/the environment to where humans are present have been detected particularly through water, although measures for this and exact transference rates need more research**. Where humans and animals are drinking or bathing in the same water, they are therefore exposed to the same bacteria found in the water. Additionally, according to Interviews, transmission between animals and the environment is typically an issue found in small family and subsistence farms in African contexts where proximity of animals to humans is much closer. However, as demand for animal products increases, the large-scale intensive farming industry is steadily expanding in Middle Income Countries. The risk of non-compliant farming management practices and non-prudent antimicrobial use therefore further exacerbates the risk of increased antimicrobial transference rates.

Some of the key challenges in addressing this animal-human AMR link include**: i) AMR priority needs on a national level are not currently being informed by a compelling evidence base**. It is not clear which AMR R&D areas in animal health need prioritising and funding. **ii) Incomplete, low quality and limited data collation for informing on the animal health problem** locally and upwardly to central government means that policy decisions from national governments are not sufficiently informed by evidence. **iii) Monitoring appropriate use of antimicrobials and access to medicines** is limited. Appropriate access and usage of them are significant drivers of antimicrobial resistance transference, poor animal husbandry practices and socioeconomic deprivation. Survival rates of animals in LMIC farms are significantly lower than in HICs, leaving producers with reduced economic returns as further fallout from this problem. **iv) Antibiotic animal health data currently collected in LMICs is principally derived from sales of antibiotics, not actual use**. Adequate mechanisms are not currently in place to capture use data, so the data that is collected only broadly correlates to the realities on the ground. Real figures of usage are anticipated to be significantly higher, as current data does not account for the additional complexities of the unregulated distribution of antibiotic products and the availability of counterfeit products (see Section 2.7 Enabling Environment).

Non standardisation and heterogeneity of data globally results in lack of reliability and representativeness when data is being compiled in databases (e.g., by the World Organization for Animal Health (WOAH)).There is **a lack of access to technology** that facilitates data generation, analysis, sharing, and dissemination. Digital technology, internet availability, and R&D capacity to transfer and analyse data on animal health diagnoses by researchers and scientists for veterinarians and farmers on the ground are very low. These low levels hinder the rates and quality of disease detection and diagnosis, adding further to the overuse and non-prudent use of antibiotics. There is a **lack of available qualitative data such as case studies and survey data** of farming and veterinarians' decision-making behaviour. More widely available data may help inform scientists on the true extent of AMR knowledge and usage patterns**.** According to our interviews, this highly sought-after data is needed to grow the evidence base to inform understandings of influencing factors and key considerations of what is happening on the ground level. This hard-to-access information needs to be obtained and collated in areas, including antimicrobial use and biosecurity practices, as sources of information utilised for farm management to inform choices was a challenge frequently echoed by stakeholders and across much of the literature.

2.6.2 Progress

Evidence is growing around **the links between environmental AMR with animals and plants**, which is where contamination from farm run-offs is shown to be mainly driven from antimicrobial use in animals, crops and fish feed. 80% of ingested

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[107] Ibid
[108] Taylor, P. & Reeder, R. (2020): Antibiotic use on crops in low and middle-income countries based on recommendations made by agricultural advisors
[109] Ibid
[110] IDRC (2021): The Animal health AMR funding landscape: An analysis of funding patterns

antibiotic substance is excreted in active form, while animal waste containing resistant microbes might be reapplied in fields in the form of (often untreated) manure, further increasing the likelihood of development and spread of AMR in the environment[111]. Evidence suggests that pharmaceutical manufacturing discharges might lead to more environmental contamination than human waste, especially where regulations on the limits and processes to dispose pharmaceutical manufacturing waste are lacking or not implemented [112]. Efforts are being made at the individual country-level and the global level to define and recommend "acceptable" levels of antimicrobial concentrations in discharges. Environmental AMR has also become an important dimension under the JPIAMR. The road map of actions for 2024 includes working to **produce more evidence and understand the role of environment in AMR**, as well as the relative contributions from sources, knowledge transfer, translational outputs, and new solutions and strategies to mitigate risks of AMR.[113] Lastly, many countries across the globe[114] have developed **wastewater surveillance programs for COVID-19,** which experts interviewed suggest could now also be used to monitor other pathogens to prevent disease outbreaks, as well as to monitor concentrations of antimicrobials and resistant organisms.

In relation to AMR in plants, the FAO, WOAH and WHO, alongside the recent joining of the UN Environment Programme (UNEP), are active in this area **through the tripartite collaboration on AMR.**[115] A review and synthesis of scientific literature on this thematic area conducted for the "Joint expert meeting on foodborne antimicrobial resistance: role of environment, crops and biocides"[116] and hosted by WHO/FAO found that **resistant pathogens are present in approximately 25% of plant origin foods**. The FAO and WHO have recommended since 2019 that **antibiotics used for human and animal health should not be registered as pesticides**.[117]

Progress is also being made in **surveillance on the use of antimicrobials in plants**, although the progress in this area is still at very early stages and lagging behind human and animal health. Interviews reported that FAO is working towards developing a new platform to collect and analyse new, more granular data on antimicrobial use as pesticides in farms, with the aim to mirror the existing GLASS surveillance system[118] on human health. The platform will use blockchain programming for data protection and anonymised data, allowing the broader farm and scientific community to benefit from the new evidence.

There have been some positive advances in recent years in **animal data collection in LMIC contexts** in high-level national data collation and reporting through the expansion of databases and datasets that extend to coverage of this thematic strand and geographic contexts. The majority of LMICs have not historically collected antimicrobial usage data within animal husbandry, but this has recently started to change as driven by the tripartite collaboration of FAO, WHO and WOAH and by strategic investments by donors and country partners, e.g., through the UK's Fleming Fund. FAO, WHO and WOAH have collectively produced the Global Database for the Tripartite Antimicrobial Resistance Country Self-Assessment Survey (TrACSS). TrACSS captures broad information on a country's capacity, coverage, and implementation of key recommendations such as "Optimizing antimicrobial use in animal health (terrestrial and aquatic)." A total of 136 countries, representing over 90% of the world's population, participated in the 2019–2020 TrACSS.[119] The Antimicrobials in Society (AMIS) Antimicrobial Use Tracker **provides an evidence-base for longitudinal analysis of global and local trends on antimicrobial use data** in non-hospital settings from both LMICs and HICs**.** LMICs were reported to submit better quality data and information to help contextualise the dataset. Anecdotal interviews informed us that submissions of animal health AMR data on antimicrobial use are growing in number faster than human health.

The Global AMR R&D Hub launched the animal health investments component of its dynamic dashboard in 2020 which previously only covered human health data.[120] Reporting annually, the dashboard has data on investments across

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[111] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps
[112] Wellcome (2018): Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges
[113] JPIAMR (2019): Roadmap of Actions 2019-2024
[114] https://www.gov.uk/government/publications/wastewater-testing-coverage-data-for-19-may-2021-emhp-programme/wastewater-testing-coverage-data-for-the-environmental-monitoring-for-health-protection-emhp-programme
[115] The three organisations formed the "Tripartite collaboration on AMR", a large scale collaboration and commitment to tackle AMR in a multi-sectoral and One Health approach (WHO, WOAH, FAO (2017): The Tripartite's Commitment: Providing multi-sectoral, collaborative leadership in addressing health challenges)
[116] https://www.who.int/publications/m/item/foodborne-antimicrobial-resistance-(amr)-role-of-environment-crops-and-biocides---fao-who-expert-meeting
[117] FAO (2020): Antimicrobial Resistance (AMR) in relation to pesticide use in plant production
[118] https://www.who.int/initiatives/glass
[119] WHO, WOAH, FAO (2021): Antimicrobial resistance and the United Nations sustainable development cooperation framework.
[120] Global AMR R&D Hub "Announcing Launch of Animal Health AMR R&D Data – One Step closer to a One Health approach", 2020 https://globalamrhub.org/announcing-the-launch/

aquaculture, livestock and poultry which are further disaggregated into the R&D areas of capacity building, basic research, vaccines, diagnostics, therapeutics, growth promoters and 'other' products/preventives. WHO is supporting capacity in IQVIA[121] research and is part of the WOAH's Global Database on Antimicrobial Agents Intended for Use in Animals network which is collecting animal health data across Africa and Asia, with the Fleming Fund also being part of this network. In 2020, 160 WOAH member countries reported they used antimicrobials in animals, up from 130 in 2016.[122] FAO-STAT provides information on AMR livestock and fish production. **New data are being submitted and analysed to provide additional evidence-based insight:** for example, currently the WOAH are developing an interactive and automated system, which will give countries the ability to not only enter their own data, but also analyse, manipulate, and present the data. This indicates a positive shift towards a more participatory approach by countries and the recognition of the value of data in its interpretation and application at national levels. As one stakeholder commented, progress is slow, but trends indicate **countries are beginning to analyse and benefit from their own data.**

WOAH's 2021 global report headline finding was the **decreasing trend in antimicrobials used in the animal sector** – down 34% from 2015 to 2017, suggesting more prudent and responsible use of antimicrobials in the animal health sector.[123] Quantities and usage are being monitored for antimicrobial agents in food-producing animals and in aquatic animal habitats such as shrimp farms. The 2021 report received the highest number of participating countries from WOAH member and non-member countries, with 160 in total, of which 133 countries were reported as submitting improved quality of quantitative datasets. This demonstrates increased engagement from participating countries and capability to measure national trends.

2.6.3 Gaps related to evidence-informed decision making in plant, environment and animal health innovation and access

Environment and Plants

Desk research and Interviews confirmed **that environmental contribution to AMR is potentially the least understood** among the One Health dimensions. Interviewees advised us where improved evidence is needed around the following areas to inform decisions and target interventions to the most impactful areas as noted below:

The scale of contamination and the relative contributions of different sources of antibiotics and antibiotic-resistant bacteria in the environment and in plants. Pathways of environmental contamination are well evidenced (human/animal waste, manufacturing discharges, crop pesticides), but the scale of use, implications of different concentration levels are not well evidenced.[124] Survey respondents confirmed the lack of evidence relating to these areas is a key gap, with 86% rating this as a high/very high priority.

The lack of surveillance and standardised methods to monitor AMR in the environment. Further surveillance and monitoring systems are needed to detect high antibiotic concentrations in the environment, with standardised methods of measuring manufacturing discharges also required.[125] More evidence is also necessary to define what are "acceptable" or "safe" levels of manufacturing discharges. Similarly, in plants, a lack of surveillance is the main hurdle in producing more evidence and improving our understanding about the use of antimicrobials. Many countries lack monitoring and surveillance, and few studies have been conducted, however FAO is working on a global surveillance system to improve the collection and analysis of data.

The human health impact of environmental contamination and antibiotic use in plants. There is inconclusive evidence about the risk and effects of environmentally transmitted AMR to humans. The lack of conclusive evidence is a major knowledge gap especially in LMICs due to the difficulty of tracing back the cause of deaths. In total, 86% of survey respondents said that research to improve understanding of the effects of environmental contamination on human health is a high/very high priority. Similarly, in plants, we still do not know whether AMR can be spread to humans through crops and especially through consumption of vegetables/fruit. Most survey respondents (63%) found that producing more evidence on the volume of antimicrobials used as crop pesticides and understanding their effect on human health is a high/very high priority.

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[121] IQVIA is a leading global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry
[122] WHO, WOAH, FAO (2021): Antimicrobial resistance and the United Nations sustainable development cooperation framework.
[123] WOAH (2021): Fifth WOAH Annual Report on Antimicrobial Agents Intended for Use in Animals
[124] Larsson, J., et. al. (2018): Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance
[125] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps

Animals

There are major knowledge gaps around antimicrobial use in animals across different LMIC farming and agricultural contexts, as well as gaps in measures to monitor and track antibiotic usage patterns to aid decision making at government policy, One Health, and R&D intervention levels. The following priority areas to improve animal health evidence should be examined:

- Capacity building and localised investment in data collection is a key area requiring resourcing and prioritising. Further work is needed to define what to measure and how, and to identify tools that are both robust and practical for most appropriate data collation and interpretation. Sufficient methods for data collection relates to the gap in measures to monitor and track antibiotic usage patterns, and gaps in knowledge and understandings of applied antimicrobial use in different animal husbandry LMIC contexts.
- More data sharing is needed in i) bottom-up data collection and monitoring the appropriate use of antimicrobials and access to medicines ii) top-down sharing of knowledge and best practices on animal husbandry, biosecurity, antimicrobial alternatives, and prudent use dissemination from experts that is accessible and bridges the digital divide. Interviewees were divided as to the extent that further data requirements should be prioritised. On the one hand, some interviewees stressed that more should be known around antibiotic use in order to refine animal management choices, to improve vaccine decision-making and reduce antibiotic use overall. However, several interviewees thought a far greater impact would be gained in investing instead into the major contributing factors that would facilitate an enabling environment, for example poor sanitation/WASH practices and improved hospital hygiene practices to mitigate the spread of resistant genes and microbes.
- Better data on the extent and patterns of usage of antibiotics as a growth promoter and in animal feed. There are major concerns in the animal health and agriculture sectors around the mass medication of animals with antimicrobials that are critically important for humans, for example with third generation cephalosporins and fluoroquinolones, colistin, tetracyclines, and macrolides.[126]
- Tracking levels of AMR across sectors. Transmission across the human, animal, and environmental interfaces can be monitored by tracking the levels of resistance mechanisms, such as extended spectrum beta-lactamase (ESBL) in animals, the environment, and human carriers, and those with ESBL-producing *E. coli* infections (e.g., the Tricycle protocol[127]). Further research could be undertaken in this area to increase understanding of these issues.[128]
- A focus on the low-level status of aquaculture within animal health. There is insufficient data and evidence on aquacultural practices and use of antimicrobials – particularly in proportion to growing consumer demand in this area. There is insufficient information on the true status of the aquaculture industry at a global scale, an industry that is set to grow even further. Another challenge is that the current R&D and investment focus of AMR and alternative practices is predominantly in livestock rather than aquaculture despite the projected growth in aquaculture.
- The compelling need to study the human behaviour and influencing factors impacting decision-making around antibiotic use. The FAO describe these as the "anthropological, behavioural, sociocultural, political and economic factors;" (see Section 2.7).

2.7 Plant, Environment, and Animal health: Enabling environment

2.7.1 Challenges

Environment and Plants

There are several challenges regarding the enabling environment for R&D on environmental AMR. Overall, national and global funding is very limited, as only 3% of AMR R&D funding goes to environment and plants.[129] Regarding regulation, there are no internationally-agreed standards for wastewater limits for antimicrobials, manufacturers are not required

[126] McEwen, S., A., Collignon, P., J. (2018): Antimicrobial Resistance: A One Health Perspective
[127] The Tricycle protocol enables countries to implement a National Integrated Surveillance System on antimicrobial resistance.
[128] Ibid.
[129] The Global AMR R&D Hub (2021): Annual Report 2021: The Global AMR R&D Funding Landscape

to disclose information about API discharges in wastewater, and regulatory agencies do not collect data on this.[130] With regard to antimicrobial use in plants and in animals, it is also the case that **regulations and their application in practice differ dramatically across different LMIC settings**. Antimicrobials are still being used in great quantities in horticulture, agriculture, and animal husbandry, while conflicting incentives and socioeconomic factors can weaken the effectiveness of stewardship interventions in LMICs. [131] For example, underpaid veterinarians or shopkeepers/market sellers may benefit from supplementary income from drug sales, and regulations may be inadequately enforced.[132] Lastly, according to interviewees, there seems to be **limited awareness of environmental AMR by day-to-day workers in these industries,** and even less regarding the prudent and appropriate use of antimicrobials in plants and animal husbandry. Interviews with stakeholders showed that even experts in the field of AMR only recently became aware of the challenges with the use of antimicrobials as pesticides. This lack of awareness in expert and scientific communities poses a significant challenge for further work in these areas.

Animals

The funders who invest in animal health AMR R&D are **highly concentrated in a few countries.** Most of the funding related to LMICs **does not go directly to research institutions in LMICs but rather to those in HICs.**[133] **This risks that the AMR priorities of LMICs do not receive sufficient funding**. Farmed animals remain a key focus for animal health AMR R&D, with livestock-associated projects accounting for close to half (41%) of the total animal health sector, with poultry at around a quarter (23%).[134] **As little as 5% is currently being invested into aquaculture**. This is a concern given the rise in fish-farming and global trends indicating diets will increasingly include fish and shellfish in the future.

At the national level for LMICs, competing public health priorities, **lack of funding and limited capacities** are impeding progress in turning plans into action. The mechanisms and capacity for One Health collaboration across government ministries and regulatory authorities in the agriculture/aquaculture/animal husbandry sectors are insufficiently resourced or not sufficiently prioritised in many contexts, with inadequate mechanisms for monitoring and enforcement. **Low levels of political awareness and commitment**, **and lack of informed representatives to champion a One Health approach are additional challenges for this sector.** Many countries lack a compelling narrative to engage policymakers and the public in a way that links antimicrobial use to core national health and economic interests. Insufficient data on the extent and nature of the problem further contributes to the lack of a compelling narrative. Many countries have included plans to improve regulatory mechanisms as part of their National Action Plans (NAP) on AMR but legislative enforcement and regulation tends to be weak. The NAPs are the prime responsibility of a government at a domestic level and interviewees report that external support is often required to make progress on NAP implementation.[135]

There is often a lack of enforcement of regulatory mechanisms when they do exist. Even where processes and guidelines are in place, the challenges are compliance, monitoring and, if necessary, enforcement. This point was reinforced throughout interviews, for example that, "There's no point, regulating something if you can't monitor compliance." Furthermore, "The presence or absence of legislation doesn't mean that something is or isn't happening." A final interviewee's comment was that "The reality is that if you're designing regulatory systems to manage and ensure they are meeting the standards they've signed up to, it's got be based on the capability of the country to be able to supervise and monitor compliance with that regulation and legislation".

HICs have access to greater resources to invest in funding of interventions and approaches which may not be applicable or are yet to be translated into LMIC contexts, with this being noted in interviewees and in the general literature. In some

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[130] Wellcome (2018): Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges
[131] Manyi-Loh, C., et al. (2018): Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications
[132] Wadoum, R. E. G (2016): Abusive use of antibiotics in poultry farming in Cameroon and the public health implications
[133] As a share of the animal health research investments included in the database, less than one third involves LMICs, amounting to USD 301 million since 2017. This represents 364 investments, 118 of which are currently active. Type 1 Investments [Funders based in LMICs funding animal health R&D in LMICs]: Data indicates funders based in LMICs support 12% of all investments in animal health AMR R&D in the dynamic dashboard and account for 2% of total funding in this area. Brazil is the leading investor in animal health AMR R&D by number of investments (49% of all Type 1), followed by China (38%), and Argentina (7%). Type 2 Investments [Funded by HICs, led by LMIC-based research organisations]: Investments made by funders based in HICs and directed at research organisations based in LMICs make up 2% of all investments in animal health AMR R&D and 2% of all funding in this area. This is the least common of the three LMIC-related investment types. In addition the funders contributing in this area are predominantly the UK, Canada, the EU and a few other European HICs. The research organisations to whom this funding is directed are predominantly based in Sub-Saharan Africa (54% of investments) and Asia (32%) (The Global AMR R&D Hub (2021): Annual Report 2021: The Global AMR R&D Funding Landscape)
[134] Ibid
[135] AMIS (live): Antimicrobial Use Tracker

cases, limited resources have meant LMICs have fewer options than would ideally be the case for investment to scale up, replicate and adapt existing interventions from HICs into LMICs. Therefore, the use of antibiotics including Highest Priority Critically Important Antimicrobials (HPCIA) for growth promotion and preventative group treatments (i.e., metaphylaxis) remain permitted in most LMICs.

2.7.2 Progress

At the global level, **awareness of AMR in the environment and animal sectors has been progressively rising** among stakeholders including scientific community, although less so for the plant sector. Environmental and animal AMR is increasingly being mentioned in G7 and G20 discussions and included in the UN broader environmental agenda and AMR policy documents.

At the country level, there have been **some awareness-raising successes.** There are now **nine designated International Reference Centres with a wide focus on AMR specifically in animal health, aquaculture, and environment globally.** The Fleming Fund has invested in the UK centre, contributing to the partnership with the UK Department for Environment, Food and Rural Affairs (DEFRA) Group agencies - the Animal and Plant Health Agency (APHA), the Centre for Environment Fisheries and Aquaculture Science (CEFAS), and the Veterinary Medicines Directorate (VMD). The partnership focus is to improve the balance of the One Health approach and take the necessary steps to improve the animal and environmental surveillance for AMR.[136] The centre provides technical assistance, training, and quality assurance to help increase AMR surveillance. The partnership is tasked with implementing the current 2021-2025 FAO Action Plan on AMR, with one of the five key objectives of the Plan being to help focus efforts and accelerate progress by "Increasing stakeholder awareness and engagement to foster change".[137] Of the nine centres, three are based in LMICs – Thailand, Senegal and Mexico.[138] **These Reference Centres support members by raising awareness of AMR and their programmes**; developing laboratory, surveillance and epidemiological capacity, strengthening governance, and promoting good practices as well as responsible use of antimicrobials.[139] Activities also being conducted through these Centres include research on innovation and incentives in food and agriculture. There is also a **large-scale roll-out of global AMR training** programmes in LMICs conducted by Health for Animals[140] and partners. **Health for Animals have been leading knowledge training programmes across Africa and Asia Resource centres**[141] on AMR and animal health in order to inform and influence changes in practice and ways of working. This training is delivered through the international efforts of private sector organisations, and the veterinary pharmaceuticals industry, along with funding from the Bill and Melinda Gates Foundation, Wellcome Trust, and the Fleming Fund.[142] The principles behind Health for Animals approaches include building in-country capacity and ensuring knowledge sustainability, for example through their "train-the-trainer" programmes. This global training roll-out has trained over 650,000 vets on responsible antibiotic use in the last three years.

On the regulatory side, Health for Animals' most recent Global Benchmarking Survey (2020) reports **progress made towards greater conformity with international benchmarks** in regulatory practices and the regulation of veterinary medicinal products of its members. Data submitted was largely from HICs but included data from MICs (Brazil and India). Datasets are being collected and reported globally which capture progress towards improving responsible use and actions undertaken to address AMR in the period of 2019 – 2025.[143] The tripartite collaboration[144] reported in 2021 that **77% of the member countries had introduced regulations on prescriptions and sale of antimicrobials** for animal use, 56% reported new policies in place to optimise the use of antimicrobials in animal health, and 63% said they had laws prohibiting the use of antibiotics for growth promotion in animals.[145] On a country level, for example, in 2020 China's Ministry of Agriculture and Rural Affairs prohibited the production, import, trade and use of growth-promoting antimicrobials.[146] This followed on from the 2017 **total ban on the use of colistin in animals as a growth promoter upon the** discovery of bacteria carrying gene mcr-1 – which can confer resistance to the antibiotic colistin – in both animals and

[136] Fleming Fund (2018): The Fleming Fund launches the International Reference Centre for AMR
[137] FAO (2021): The FAO Action Plan on AMR 2021-25
[138] https://www.fao.org/antimicrobial-resistance/resources/reference-centres/united-kingdom/en
[139] See https://www.fao.org/antimicrobial-resistance/resources/reference-centres/mexico/en/and https://www.gob.mx/senasica
[140] Veterinary pharmaceuticals industry body
[141] The Global AMR R&D Hub (2021): Annual Report 2021: The Global AMR R&D Funding Landscape
[142] Members of Health for Animals represent approximately 90% of the Animal Health sector, covered by ten major pharma companies.
[143] Health for Animals (2020): Global Benchmarking Survey
[144] WHO, WOAH, FAO (2021): Antimicrobial resistance and the United Nations sustainable development cooperation framework.
[145] AMR Industry Alliance (2018): tracking progress to address AMR
[146] The Lancet (2021). Banning colistin in feed additives: a small step in the right direction

patients in China, and its subsequent spread overseas.[147] In 2019, following the recommendation of the Drugs Technical Advisory Board for the prohibition of colistin and its formulations, **India and Brazil also introduced a colistin-ban** for food-producing animals, including poultry, aquafarming and animal feed supplements.[148]

There has been further reported success with regards to regulatory efforts targeting AMR in the **global efforts to recommend targets for "safe limits" in antimicrobial manufacturing discharges**. In 2018, the AMR Industry Alliance brought together 100 biotech, diagnostic, generic and research-based pharmaceutical companies to discuss a single framework[149] that promotes responsible antibiotic manufacturing. The resulting recommendations[150] are a positive step towards reducing discharges, protecting the environment from contamination, and preventing resistance to develop and spread further. It is worth noting, however, that these are recommended limits, with reporting against these limits being voluntary, and participants are only required to report whether the target is met and not any actual level achieved. In addition**, the feasibility of applying discharge limits can vary significantly across LMIC settings. The cost of reducing discharges is not yet clear** (and will again vary across different settings), meaning that governments and stakeholders will have to consider the right legal, economic, and social incentives for manufacturers to comply.

Multinational pharmaceutical companies are also starting to require their **LMIC-based API suppliers to follow targets on discharge limits,** as well as report on their compliance with the targets**.** A recent benchmark report (Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark (2021) found progress in this area as the number of pharmaceutical companies requiring their API suppliers to set limits has risen (from three out of ten in 2018 to ten out of 17 in 2021).[151] However, there are still gaps in tracking and monitoring compliance with these limits on suppliers' sites, with the report noting that only 20% of sites measure levels to ensure compliance, while only 5% of suppliers' sites were reported as truly compliant. Moreover, industrial discharge of APIs into the environment in some middle- and low-income countries is not sufficiently regulated.[152]

Reports show that **30-40 countries have some form of regulation in place to control the use of antimicrobials in plants.**[153] This includes countries where antimicrobials might still be allowed but oversight is strong and their use in practice is minimal. Antibiotics are effectively prohibited for the control of plant diseases in the UK and the EU, although it is reported that "some European Union (EU) members (Austria and Hungary) authorise their emergency use to control outbreaks, but the volumes used are negligible and their application is strictly controlled".[154]

2.7.3 Gaps related to the enabling environment in plant, environment and animal health innovation and access

The main gaps regarding the enabling environment in plant, environment and animal health are around the availability and focus of new **funding**, and applying achievable **regulations**, **raising awareness and other mechanisms to change behaviour** such as training, social and behaviour change communication, incentives, and alternative solutions to antimicrobials.

There is a need to **invest more finance in the animal health strand,** while also taking a more holistic approach across all strands, particularly with regard to pathogen and AMR transmission. Advances made on the human health side will be stymied if developments are not linked to the wider environment and influence of antimicrobial use in animals. In addition, current funding patterns in animal health show that **the subset of funders who invest in animal health AMR R&D is highly concentrated in a few countries**. As outlined in the earlier report in Challenges Section 2.8.1, most AMR funding currently does not go directly to research institutions in LMICs but to those in HICs. This risks that the AMR priorities of LMICs do not receive sufficient funding.[155] Evidence from multiple Interviews across plant, environment and animal health suggests that **new funding should be prioritised for researching and applying innovative solutions and making use of new and existing technologies** (see Challenges Section 2.8.1).

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[147] The Global AMR R&D Hub (2021): Annual Report 2021: The Global AMR R&D Funding Landscape
[148] London College Imperial (2019): "Indian Colistin ban in animal welfare major step in fight against AMR"
[149] https://www.amrindustryalliance.org/shared-goals/common-antibiotic-manufacturing-framework/
[150] Tell, J., et al. (2018): Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations
[151] Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021
[152] Pharmaceutical Wastewater Effluent-Source of Contaminants of Emerging Concern: Phytotoxicity of Metronidazole to Soybean (Glycine max) (2017)
[153] Stockwell, V., O. & Duffy, B. (2012): Use of antibiotics in plant agriculture
[154] Ibid
[155] IDRC (2021): The Animal health AMR funding landscape: an analysis of funding patterns

On regulation of manufacturing discharges and use of antimicrobials in crop protection, 60% of survey respondents said that applying regulatory limits on the use of antimicrobials in plants is a high/very high priority and 67% of respondents said that applying regulatory limits on acceptable levels of pharmaceuticals manufacturing discharges is a high/very high priority. However, a key challenge is the lack of information about the feasibility of applying limits in different LMIC settings, with this highlighting the need for research to evaluate the feasibility and cost of adhering to discharge targets, and for work identifying and evaluating incentives to reduce discharges in a timely and effective way.[156] Interviewees also suggested that new funding should be directed towards establishing standardised measures and better monitoring of both manufacturing discharges as well as antimicrobial use in plants.

There are also gaps in regulation in antimicrobial use in animals and sales of unregulated or counterfeit products. The regulatory environment is a domestic issue and hence is ultimately the responsibility of each country. Interviewees recommend an increased focus on those LMIC countries who commit to change and can demonstrate the required capability and capacity to do so. External actors or institutions can address gaps in regulation through a partnership approach that delivers knowledge sharing, capacity building and guidance for receptive LMICs. As highlighted in one interviewee "Surely it's better to work with organisations to transition from where they are to where they need to be, and that's a process…. When thinking about working with low-income countries, we need to work with them, not set them up to fail." Whilst some stakeholders stated that increased regulatory enforcements would be beneficial, most felt this was not a practical gap to fill in an LMIC from an external non-government intervening perspective. These stakeholders felt more strongly that alternatives to regulation and enforcement through incentive approaches and the aforementioned guidance offered by HICs would enable a more suitable and sustained transition on a domestic scale.

There are several gaps identified in awareness raising on environmental AMR issues. The tripartite collaboration self-assessment survey has identified many of those gaps, with plants, food production, food safety, and environment given the lowest ranking in terms of awareness-raising activities.[157] The majority of survey respondents ranked activities in these areas as "level one", which means "no significant awareness-raising activities on relevant aspects of risks of antimicrobial resistance" or "level two", which indicates "some activities in parts of the country to raise awareness about risks of antimicrobial resistance and actions that can be taken to address it". A significant proportion of respondents did not respond at all to these questions (as opposed to when asked about human or animal health), which could further indicate a lack of awareness.

There is a need to facilitate the cross-sharing and collaboration of research findings and interventions which extends to LMICs in order to increase country level awareness around animal health. "Strengthen research coordination and collaboration is part of the need to innovate to secure the future" was recommended by the UN Interagency Coordination Group (IACG) 2019 final report to the UN Secretary General. As noted by one interviewee, LMICs need to have more leading roles. LMICs felt that the global response to AMR is driven by a small group of mostly HICs, with little room for LMICs to shape the global agenda around awareness and intervention design and uptake. Capacity building, partnership and joint working is crucial to enable the development and investment of LMICs' response to AMR, which HICs, external institutions and key players could respond to. In addition, research findings need to be disseminated in an accessible way so they can be used on the ground, and recommendations and observations should relate to operational uptake of prudent antimicrobial use and biosecurity practices in animal health. Data may be shared in reports at institutional level and national level, but it was felt that this is not translated into application and interventions regularly, and sufficiently quickly. As noted in one interview, "Funding needs to go into the spread and uptake of data into practice". There remain gaps in more resources, awareness-raising education and information dissemination to farmers and vets on the optimised use of medicines, particularly the use of antimicrobials in animals (and plants). Veterinary oversight is also needed from vets/paraprofessionals/trained animal care workers. A stakeholder interviewee shared with us, "What I hear and what I experience is that there is a lot of data being collected, a lot of resources going into this, but it's not really used very much for action, it's just used to be reported to WHO or to another entity. I see there is the need for something that's far more agile and much smarter to transmit data for applied use".

Interviews questioned if focus on awareness-raising alone would be sufficiently impactful, without the simultaneous delivery of interventions that disseminate antimicrobial alternatives and incentivise prudent antimicrobial use. The addition of these interventions will be best informed by closer study and understanding of existing social and behaviour change to determine the responses and precise alternative investment areas necessary to change behaviours and steer practitioners away from non-prudent antimicrobial use. The tripartite collaboration self-assessment survey also found

[156] Wellcome (2018): Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges
[157] WHO (2018): Monitoring global progress on addressing antimicrobial resistance

that training and professional education on AMR in the areas of farming, food and environment was low, with **67 countries (44%) not having had training on AMR for key stakeholders on these areas.**[158] The survey showed that G20 countries and HICs are further along on implementing training than non-G20 and lower-income countries. **Social behaviour change communication interventions** has also been found to successfully influence user behaviour. Financial incentives could take the form of **subsidised and reduced costs of appropriate disease prevention and control tools in LMICs** and/or **incentives in animal husbandry/aquaculture management industries** to change practices away from the use of antibiotics. Further relevant **research into antibiotic alternatives and animal vaccines is also a priority. Viable antibiotic alternatives and measures** are needed to increase agricultural productivity in LMICs, and "pull" farmers towards non-AMR use in addition to education, rather than relying on "push factors" of sanctioning and health warnings.

Finally, there is a need to consider **gender equality and social inclusion for animal and environmental AMR more fully.** These are largely overlooked priorities in health and development agendas and when researching behaviours and patterns of antimicrobial use in animal health and farming. Women living in LMICs are more likely than men to face additional barriers and disadvantages around AMR issues. Firstly, women predominantly manage the small-scale production of certain types of livestock. Secondly, women may also face financial, literacy, mobility, or other systemic gender-based barriers to accessing veterinary services for their livestock. These barriers affect knowledge of AMR, and access to and ownership over AMR containment resources. At present, factors such as gender and possibly other social considerations, are rarely an explicit focus of the current research being undertaken in the area of AMR R&D.[159]

2.8 Plant, environment, and animal health: Innovations and interventions in environmental contamination and use of antimicrobials in plants and animals

2.8.1 Challenges

Environment and Plants

One of the major challenges in environmental contamination is the **lack of evidence to develop targeted and evidence-based interventions,** especially in LMIC settings. Interventions need to address multiple pathways to contamination: human/animal waste, pharmaceuticals , agriculture/farming where **antibiotic residues are released into the environment and bodies of water either through waste water/sewage, farm run-off or manufacturing effluent.** Although this is a widely known concern there are low levels of research being conducted in this area, resulting in limited evidence about the scale and contribution of each intervention. This lack of evidence makes it difficult to select the most effective approach. There are also **cost considerations** in treating high concentrations of antimicrobial substances and antimicrobial-resistant bacteria at a few locations (e.g., pharmaceutical effluent) as opposed to treating low concentrations at many locations (e.g., all municipal wastewater facilities). [160]

There are also challenges in the **effectiveness and uptake of existing interventions for plant and animal health**. Interventions on environmental contamination include regulation in wastewater limits as well as different waste management solutions and treatments. A 2016 study[161] examined the effects of wastewater treatment on antibiotic concentrations from rural and urban hospitals and found concentration was only partly reduced after treatment. Wastewater treatment plants (WWTPs) have historically shown varying degrees of success in measuring and removing antibiotic residuals while a recent systematic review found that 118 studies have reported **a partial efficiency of waste water treatment plants (WWTPs) to reduce antibiotic resistance in treated discharges.**[162] One of the major challenges is

[158] WHO (2018): Monitoring global progress on addressing antimicrobial resistance
[159] IDRC (2021): The Animal health AMR funding landscape: an analysis of funding patterns
[160] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps
[161] Lien, L. T. Q., et al. (2016): Antibiotics in Wastewater of a Rural and an Urban Hospital before and after Wastewater Treatment, and the Relationship with Antibiotic Use-A One Year Study from Vietnam
[162] Goulas, A., et al. (2020): How effective are strategies to control the dissemination of antibiotic resistance in the environment? A systematic review

that **typical treatment plants are not specifically designed to remove pharmaceuticals and antimicrobials**,[163] which means that more specialised treatment methods need to be used, for example biological treatments.[164]

Even if an intervention is effective, **innovative interventions cannot be simply transferred from HICs to LMICs.** Their uptake can be constrained due to LMIC resource and skill limitations and/or incentives to apply the interventions. As for AMR in plants, interviewees suggest that **socioeconomic factors are a crucial determinant in the uptake of crop protection alternatives to antibiotics,** given how inexpensive and easily accessible antibiotics are in LMICs compared to, for example, alternative pesticides, diagnostics, and preventative measures (e.g., better sanitation, pesticide management systems, etc.).

Similar challenges were identified by interviewees in animal-related interventions and innovations. **A few interviewees highlighted that there are not enough economic incentives thus hindering R&D of new animal vaccines and antibiotic alternatives**. Costly and lengthy development of vaccines and antibiotic alternatives demand economic/other incentives to make R&D in this area a worthwhile and profitable investment. For tools that already exist, there are **challenges in the transfer of knowledge, innovations, and interventions from HICs to LMICs**, and in the adaptation and use of these within LMIC contexts. Many interviews said that new antimicrobials would not be the most effective intervention to tackle AMR in the environment and animals, and the focus should instead be on social and behaviour change communication interventions, preventative measures, and alternative management solutions.

The need for AMR interventions in food-producing nations is set to grow. As lifestyles in LMICs adapt to rising incomes, global demand for affordable meat will rise. The rise in global demand for protein will lead to an increase in production and supply. Most notably in the number of poultry factories in MICs, such as India, and bovine and pork factories in Latin America[165] and China.[166] The increasing number of factories will have considerably impacts across animal, plant and environment. By volume, more antimicrobials are used for animals than for humans, especially for rearing livestock and, where permitted, for growth promotion or prophylactic group treatment. Clear transmission pathways have enabled researchers to link excessive use of antimicrobials in animals to the development of AMR in humans, both through the transfer of antimicrobial resistance genes and via zoonoses.[167] Antimicrobial use in aquaculture is also growing due to the global rise in consumption of fish and crustaceans. Use of antimicrobials in animals, both terrestrial and aquatic, can have significant second-order impact on environmental contamination with antimicrobials through e.g., fish farms and farm run-off[168]

Lastly, **challenges have been identified around the availability of measures to detect the presence/levels of AMR** in plants, the environment, and animals. Evidence suggests that LMICs face severe barriers when it comes to low-cost, readily available technology[169] and universal/standardised AMR monitoring indicators. On-site identification is not possible without knowledge, internet access and technological tools that can link the field to a laboratory.

2.8.2 Progress

Environment and Plants

Several interventions and strategies for **managing AMR-relevant manufacturing and medical waste are available**.[170,171] Examples include incineration, which is potentially the most complete method (although it is resource-intensive), as well as disinfection and chlorination in WWTPs. The literature also highlights a list of innovative methods, for example microbiological treatment, enzymatic treatment, chemical treatment, adsorption (removing organic compounds by partitioning them from an aquatic phase to solid), photocatalysis, UV light methods, electrochemical degradation, and

[163] SIWI (2018): Antibiotic resistance: The importance of water
[164] Branchesme, F. & Munir, M. (2018): Strategies to Combat Antibiotic Resistance in the Wastewater Treatment Plants
[165] https://www.fao.org/americas/priorities/produccion-pecuaria/en/
[166] https://www.fas.usda.gov/data/china-livestock-and-products-annual-6
[167] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps
[168] Lo Yan Yam, E., et. al (2018): Antimicrobial Resistance in the Asia Pacific region: A meeting report
[169] For example, "Mologic" is a leading developer of lateral flow and rapid diagnostic technologies, products and services. They are working with companies, researchers and clinicians to help them deliver fast, reliable and accurate diagnosis at the point-of-care. Through Social Enterprise funding their aims are to expand affordable access to state-of-the-art medical technology in LMICs. Sister company Global Access Diagnostics (GAD) focus on low-cost manufacturing of diagnostic tests, and licenses Mologic's technology in Africa and South Asia.
[170] Branchesme, F. & Munir, M. (2018): Strategies to Combat Antibiotic Resistance in the Wastewater Treatment Plants
[171] Wellcome (2018): Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges

others. However, new concerns are raised regarding innovative waste management methods as some can be significantly more expensive than common practices, thus less applicable to LMICs.

Some progress has been made in recent years in terms of **preventive measures to reduce the presence of antimicrobials in waste and ultimately in drinking water.** There have been attempts to prevent inappropriate disposal practices such as flushing unwanted medicines down toilets and sinks, which can contribute to contamination in the environment. However, preventative measures such as regulation and guidance, pharmaceutical take-back programmes and raising consumer awareness have mainly been limited to the UK, EU, US, Australia, and Canada, and have generally not been implemented in LMICs.[172]

With regard to mitigating **AMR in plants,** strategies have included mathematical modelling to predict high-risk periods for crop disease, practices to reduce the spread of crop pathogens (e.g., integrated pesticide management systems[173]), and diagnostic tools and alternative treatments to reduce disease. However, the uptake and utility of these strategies is still questionable, since "No effective interventions to limit farm run-off have been observed so far, apart from bans on the 'inputs' (i.e., limits on the purchase and use of antimicrobials in farm settings)" according to the Wellcome Trust report[174].

Interviews also pointed to the **potential effectiveness of social and behaviour change communication interventions to prevent AMR development and spread in plants**. As farmers often buy pesticides and antimicrobials/growth promoters from agricultural/veterinary stores, applying **measures and guidelines** in stores could potentially reduce the volume of antimicrobials sold and used in farms. An example of such interventions currently being developed by FAO is **warning labels** on pesticide and antimicrobial packaging, as previously implemented on antibiotic labelling to prevent excess use in humans. Simple warning labels already exist in the EU, US and other HICs, but not in LMICs. The goal of these labels is to inform agricultural and veterinary professionals who sell antimicrobials, but also to raise awareness of the dangers of excess use and misuse of antimicrobials in plants among farmers.

Animals

Progress in animal health AMR is slow, as funding and time constraints have limited R&D progress. Our research did not uncover substantial developments in this area, although there have been a few areas of progress in tangible products (therapeutics, vaccines, diagnostics).

Three key examples of antibiotic animal health alternatives currently in development:

- Antimicrobial peptides are one of the most promising alternatives to antibiotics since they could be used to treat bacterial infections, especially those caused by multidrug-resistant pathogens. Antimicrobial peptides, with various activity spectra and mechanisms of actions could be used against ESKAPE bacteria[175] and could provide biofilm treatments, due to their synergistic activity, and as prophylactic agents. Limitations and challenges restricting therapeutic applications are being investigated to determine whether antimicrobial peptides could replace antibiotics in the near future.[176]
- Therapeutic bacteriophages (commonly called phages) can be used to manage bacterial infections in a wide range of animal organisms, including farmed fish.[177]The natural immunogenicity of phages often induces the modulation of a varied collection of immune responses in several types of immunocytes while promoting specific mechanisms of bacterial clearance. However, to achieve standardised treatments at the practical level and avoid possible side effects in farmed fish, more comprehensive understanding of the biology of fish and the associated genomes is

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[172] WHO (2011): Pharmaceuticals in Drinking-water

[173] Pesticide management systems could provide complete and effective solutions to manage the volume of antimicrobials used in farms and prevent potential outbreaks. Examples of these management systems already exist, such as the Plantwise Online Management System, which is a good first step towards managing disease and tackling AMR in plants in the future. While this could be implemented more broadly to achieve better global coverage, the system provides a digital toolkit for farmers to learn and apply sustainable practices in crop production, and to import and analyse data on pests to manage disease and prevent outbreaks. Data is also reported back to Plantwise, where it is analysed in research studies, enriching the evidence base on crop disease and management. (https://www.plantwise.org/)

[174] Wellcome (2020): The Global Response to AMR: Momentum, success and critical gaps

[175] The acronym ESKAPE includes six nosocomial pathogens that exhibit multidrug resistance and virulence: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. Persistent use of antibiotics has provoked the emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) bacteria, which render even the most effective drugs ineffective (source https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6452778/)

[176] Rima, M., et al. (2021): Antimicrobial Peptides: A Potent Alternative to Antibiotics

[177] Ramos-Vivas, J., et al. (2021): Phage Therapy as a Focused Management Strategy in Aquaculture

required. The current functional use of phages against bacterial pathogens of farmed fish, swine and poultry is still in its infancy.[178, 179]

- A third alternative to antibiotics undergoing R&D is yeast (Saccharomyces cerevisiae). The ban on the use of antibiotics in feed for broiler chickens in some parts of the world, coupled with increasing consumer demand for 'antibiotic-free' poultry products, has increased the interest of poultry researchers and producers in identifying suitable alternatives to antibiotics. A review in the Journal of Applied Poultry Research discusses the possibility of using probiotic and prebiotic yeast to increase productivity in healthy or disease-challenged broiler chickens.[180] There is convincing evidence that probiotic and prebiotic yeast products can replace in-feed antibiotics in broiler chicken production, but more testing is needed to achieve consistent results. A combination of appropriate yeast products alongside proper husbandry practices and biosecurity measures could significantly maximise broiler productivity and may pave the way to a global antibiotic-free era in meat production.

There has been some progress in vaccine development in animals, most notably through the endeavours of the STAR-IDAZ International Research Consortium on Animal Health, GAMRIF, IDRC and WOAH, although further research is required. Analysis of the literature revealed that animal health in the farming industry is an area of immediate potential for impact in the AMR context and it is being highlighted by WOAH as a priority gap. WOAH has published reports of two meetings where they outlined the priorities for developing vaccines for AMR in animals.[181]

There has also been progress in examining the social, cultural and economic factors that have led to the non-prudent use of antimicrobials. Antimicrobials in Society (AMIS) is a Social Science and Medical Science joint initiative with the London School of Hygiene & Tropical Medicine which has been examining this area and has uncovered evidence of improving practices and behaviours. This holistic approach bringing together the clinical and the social science dimensions works within and beyond a One Health human/animal/environment approach. The AMIS programme had projects in Thailand and Uganda (2017-2021) which instigated opening the field of AMR research beyond its traditional boundaries.[182]

2.8.3 Gaps related to plant, environment and animal health innovations and interventions

In this section we summarise the key gaps in innovation and interventions for plant, environment, and animal health using survey collected data on key priorities and gaps in these areas. The plants/environment/animal section of the survey offered shortlisted priority intervention areas and asked respondents to rate them on a scale from one to five. The table below shows most of the intervention areas were rated as five (very high/critical priority)[183].

Table 4: Environmental Contamination Priorities (survey)

Environmental Contamination	Don't know/prefer not to say	1. Not a priority	2. Minor/low priority	3. Medium priority	4. High priority	5. Very high/critical priority
Apply regulatory limits on 'acceptable levels' of pharmaceutical manufacturing discharges to reduce concentrations of antibiotics	2%	0%	7%	23%	23%	44%
Research to determine appropriate standardised measures for safe levels of manufacturing discharges and monitoring	2%	0%	2%	26%	26%	44%

[178] Ibid.
[179] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9416366/ https://pubmed.ncbi.nlm.nih.gov/35579475/
[180] Ahiwe, E.U, et al. (2021): Can probiotic or prebiotic yeast (*Saccharomyces cerevisiae*) serve as alternatives to in-feed antibiotics for healthy or disease-challenged broiler chickens?: A review
[181] WOAH (2018): Report of the Meeting of the WOAH Ad Hoc Group on Prioritisation of Diseases for which Vaccines Could Reduce Antimicrobial Use in Cattle, Sheep, and Goats and WOAH (2015): Report of the Meeting of the WOAH Ad Hoc Group on Prioritisation of Diseases for which Vaccines Could Reduce Antimicrobial Use in Animals
[182] https://antimicrobialsinsociety.org/
[183] 1. Not a priority,2. Minor/low priority, 3. Medium priority, 4. High priority and 5. Very high/critical priority.

R&D into LMIC-appropriate wastewater treatment solutions to reduce antibiotic concentrations in discharges	5%	0%	5%	7%	51%	33%
Research to improve understanding of the scale of contamination and relative contribution of sources (agriculture, human/animal waste, manufacturing discharges)	0%	0%	2%	12%	35%	51%
Research to improve understanding of the effects of environmental contamination on human health	0%	0%	0%	14%	30%	56%
Produce more evidence on the impacts of antibiotic use in agriculture and aquaculture including run-off into oceans and rivers	0%	0%	2%	23%	35%	40%

Source: GAMRIF gap analysis survey

The need for implementation science to support adaptation of HIC solutions to LMIC contexts. Innovative and effective WWTP interventions exist, but their feasibility for LMICs is not clear as studies so far have been mostly lab-focused/pilots. Interviewees specifically called instead for more **implementation/operational research,** i.e., research which shows how to adapt tools from HICs to LMICs assessing feasibility, estimating costs, and considering the right incentives. In total, 84% of survey respondents said that R&D into **LMIC-appropriate wastewater treatment solutions** to reduce antibiotic concentrations in discharges is a high/very high priority.

As previously, survey results on the use of antimicrobials in plants are shown in the table below. Respondents were asked to rate a shortlist of intervention areas regarding the use of antimicrobials in plants, using the same scale (1-5). Overall, there is a bigger variance in responses for this issue compared to environmental contamination, although most respondents still rated most areas as high/very high priority. The proportion of people saying "don't know/prefer not to say" was higher in the plants section of the survey than in other areas (human health, animal health and environment). This higher proportion aligns with evidence from the interviews and document review that there is relatively less awareness about the use of antimicrobials in plants, even among AMR expert communities.

Table 5: Use of antimicrobials in plants (survey)

Plant Health	Don't know/prefer not to say	1. Not a priority	2. Minor/low priority	3. Medium priority	4. High priority	5. Very high/critical priority
Producing more evidence on the volume of antimicrobials used for crop protection as pesticides, and understanding their effect on human health	7%	0%	0%	30%	27%	37%
R&D on alternative plant protection solutions (e.g., integrated pesticide management systems) suitable for use in LMICs	10%	0%	10%	10%	43%	27%
Applying regulatory limits on use of antimicrobials in plants	7%	0%	7%	27%	33%	27%
R&D on innovative environmental diagnostic and monitoring tools (e.g., in farming to monitor antimicrobial concentrations in run-offs from pesticide use)	7%	0%	0%	27%	40%	27%

Improving surveillance of antimicrobial volumes/concentrations in the environment coming from pesticide use, at national level within LMICs as well as at global level	7%	0%	7%	23%	33%	30%
Operational research to understand how best to integrate existing mitigating solutions in current health/WASH programmes for farms to reduce the use of antimicrobials in crop plants	10%	0%	3%	17%	37%	33%
Reapplication or repurposing existing crop protection technology/innovation/research from other countries (i.e., from Europe or USA)	20%	7%	7%	17%	33%	17%

Source: GAMRIF gap analysis survey

Regarding the use of antimicrobials in plants – 70% of survey respondents felt it is a high/very high priority that there is operational research to help understand how best to integrate existing mitigating solutions in current health/WASH programmes for farms to reduce the use of antimicrobials in crop plants. Interviewees also raised the need to support better uptake of existing solutions, e.g., crop management systems, diagnostics, surveillance, and preventative measures. Existing digital technologies need to be better utilised (e.g., for crop management and detection/prevention using smartphone technology). Finally, more focus on social and behaviour change communication interventions is needed to address the social and economic factors behind the use of antimicrobials in plants.

Stakeholders appear to have mixed views on whether improving evidence or implementing interventions should take highest priority. Some suggested that surveillance should initially target the most impactful interventions, while others felt it was difficult to produce relevant evidence and instead suggested prioritising urgent action. The survey showed similar results, although more respondents tended to think further evidence was a very high/critical priority than prioritising regulatory limits and WWTP interventions. This was also true across the animal health findings.

Animal health survey findings are shown in the table below. As previously, respondents were asked to rate a shortlist of intervention areas regarding animal AMR, using the same priority scale (one-five). Overall, most respondents rated these priority areas as five (very high/critical priority).

Table 6: Animal health (survey)

Animal Health	Don't know/prefer not to say	1. Not a priority	2. Minor/low priority	3. Medium priority	4. High priority	5. Very high/critical priority
R&D on alternatives to antibiotics for animals and aquaculture	0%	0%	0%	13%	35%	53%
R&D on new animal vaccines	5%	0%	3%	15%	30%	48%
Increase uptake of existing vaccines for use in animals	13%	0%	3%	13%	30%	43%
R&D for new, low cost, effective diagnostics tools and disease identification methods, to better guide appropriate antibiotic use	5%	0%	0%	15%	35%	45%
Improve data collection activities and data sharing practices (e.g., from farmer to lab)	5%	0%	5%	28%	23%	40%

Improve coordination and facilitate knowledge sharing of best practices on animal health	5%	0%	0%	23%	25%	48%
Local level research and pilot studies on farming practices/behaviours and decision making around animal husbandry, antibiotic use and antimicrobial detection, treatment and alternative practices	5%	0%	5%	10%	40%	40%
Research to better understand transference of antimicrobials from animal to environment, and then to humans	4%	0%	0%	15%	38%	45%

Source: GAMRIF gap analysis survey

The animal health section of the GAMRIF gap analysis survey provided a shortlist of eight priority intervention and R&D areas. Respondents were invited to rank each of these to assess their priority on a five-point scale from low to high.[184] A very small proportion of respondents did not know their views on specific issues, and no respondents chose minor/low priority, indicating that it was not felt by any of the respondents that our identified gaps were not a priority in some way. The spread of the data towards the high end of the rankings suggests **broad agreement among survey respondents that the shortlist has more high priority/high impact areas than low and that these are prioritised focus investment areas**. "R&D on alternatives to antibiotics for animals and aquaculture"; "R&D on new animal vaccines "and, "Improve coordination and facilitate knowledge sharing of best practices on animal health" were considered the three highest priorities. "Research to better understand transference of antimicrobials from animal to environment, and then to humans" and "Local level research and pilot studies on farming practices/behaviours and decision making around animal husbandry, antibiotic use and antimicrobial detection, treatment and alternative practices" were also considered to be of high priority. The responses in the open text portion of the survey are generally consistent with the interviewees and literature review findings.

Interviewees and reviewed literature also pointed to the following seven gaps related to plant, environment, and animal health.

1. **Environmental and animal AMR interventions are "overly siloed".** Stakeholders suggested that interventions could be integrated into broader programmes such as those focused on IPC, water, sanitation and hygiene (WASH) or farm biosecurity. Integrating the interventions into WASH programmes would provide more cost-effective collaborative approaches to tackle AMR across One Health areas and allow proactive planning and implementation of preventative measures. An example of this could be integrating AMR components into healthcare staff training and applying guidelines on safe disposal of antimicrobial waste in hospitals and healthcare facilities. There is a need in animal health to address human behaviours and social factors impacting on the choice of antimicrobial use or alternative methods in biosecurity and farming management.
2. **Early-stage research into environmental linkages and the pathways**. Progress has been made in recent years evidencing transmission of AMR from animals to humans. It is known that **transmission of AMR from humans and animals into the wider environment comes via different routes** including from agriculture, aquaculture, hospital effluents, and human and animal waste. Clear measurement on the effect of antimicrobial use in animals, and its effects in human health, has not yet been determined. Detection of antimicrobials in water and waste has been cited as a low cost and therefore an impactful area to investigate transmission rates in the LMIC context.
3. **Furthering the development of low-cost, accessible, innovative technologies for testing animals, and alternatives to antibiotics**. Rapid diagnostics are needed for both pathogen identification and resistance testing. There is an unmet

[184] 1. Not a priority,2. Minor/low priority, 3. Medium priority, 4. High priority and 5. Very high/critical priority.

need for rapid microbial identification and decentralised diagnostic testing to aid farmers/vets via remote detection. This could significantly reduce the unnecessary use of antibiotics, and the spread of AMR. Technology needs to be contextually appropriate for LMICs, i.e., not necessarily reliant on the internet but facilitating data transfer on site. As a interviewee explained; "The need [is] for something that's far more agile and much smarter to transmit data for applied use". Possible examples of agile and smarter technologies currently under development include AST, POC Testing and smartphone-based monitoring systems. Interviews also emphasised that R&D focused on alternatives to antibiotics should be continued.

4. Testing potentially counterfeit or mis-labelled products. Pilot studies are being conducted to better understand the prevalence of counterfeit antibiotics being used by poultry farmers. The APHA has been working in Nigeria collecting empty bottles of products used by farmers and conducting lab tests of the chemicals to better understand the active ingredients being used by farmers. Scaling up this testing could generate a more accurate picture of counterfeit antibiotic usage.

5. Greater uptake of vaccines and stewardship of antimicrobials. The use and roll out of vaccines for animal health should be improved, as should the prescribing and handling of antimicrobials including the potential for faster diagnosis and better data management.[185]

6. Research addressing changing human/social behaviours, focused on leveraging wider global health agendas to generate positive externalities for decreasing the prevalence of AMR, i.e., WASH and IPC which reduce the overall need for antimicrobials. Environmental and animal AMR interventions should be rolled out with evidence-based approaches to encourage take-up and behaviour change, as was reported from a wide range of stakeholders.

7. Prevention and treatment-focused interventions in aquaculture are both much-needed and neglected areas in comparison to livestock farming. Focus is needed on managing excessive antimicrobials being discharged into the oceans and waterways because of the growing aquaculture industry. Within this, investment is needed into understanding potential mitigation measures to address non-prudent antimicrobial use in the aquatic environment. Evidence from LMICs shows that antimicrobial use is associated with a lack of diagnosis or diagnostic failure, and aquaculture producers, including suppliers, prioritise treatment over prevention and biosecurity.

[185] BBRSC, UK Research & Innovate (UKRI) – "How BBRSC Investments are tackling AMR," 2021- https://www.ukri.org/blog/stop-the-spread-how-bbrsc-investments-are-tackling-amr/

3.0 Impact Matrix: AMR interventions in LMICs where GAMRIF funds could have most impact

This section sets out the bespoke impact matrix tool that was used to analyse the identified areas of the gap analysis and assess it against the study's research questions. For each of the six thematic areas of focus we assessed six to eight key findings using four criteria, with each of the criteria being given a Red-Amber-Green (RAG) level rating[186]. Table 7 below provides an overview of the four criteria used, a description of each of them, and a description of the RAG levels.

The four criteria – 1) Alignment with AMR policy priorities and work of other AMR funders, 2) Alignment with the GAMRIF ToC & GAMRIF distinctiveness, 3) Neglected, underfunded and niche interventions and 4) potential for high impact in LMICs – were used to assess the potential impact of the AMR interventions identified in this gap analysis. Under each thematic area, there are between 6 and 8 potential AMR interventions which impact level on preventing AMR is ranked using the RAG level rating in Table 7.

The three-tier RAG scale differs slightly in its application between the first two and last two criteria. For criteria one and two, the scale of one-three (red, amber, and green) ranks the degree of alignment or how much the R&D areas fit the global AMR policy and GAMRIF's overarching AMR R&D objectives. For criteria three and four, the one-three scale draws on the gap analysis to show the availability and strength of evidence in the intervention areas.

[186] The RAG rating happens within each impact matrix, not across the 6 impact matrices. Thus, an amber box in the plants impact matrix could be more impactful/aligned than a green box in the therapeutics impact matrix and vice versa.

Table 7: Criteria used to develop the Impact Matrices

Criteria	Description	Levels
Criterion 1 – Alignment with AMR policy priorities and work of other AMR funders	Alignment with (global and national) AMR policy priorities (relevance and coherence of interventions areas with policy priorities or key areas) and external coherence (synergies with other AMR partners' work; synergies with other UK Government funded work). Policy documents considered to provide a ranking for this criterion included: WHO Global Action Plan (2015) on AMR, Tackling antimicrobial resistance 2019–2024 and Antimicrobial resistance in international development: UK Research Funding Landscape.	Level One – Limited strategic relevance to AMR priorities, including no direct mention in policy documents. However, some other organisations working in this AMR area. Level Two – Strategic relevance to AMR priorities is medium (e.g., an area that has been funded for a while) and AMR partners/government have funded for a while, but further attention is needed. Level Three – Good strategic relevance. It is mentioned in policy documents reviewed and partners working intensively in this area for many years.
Criterion 2 – Alignment with the GAMRIF ToC & GAMRIF distinctiveness (internal coherence)	Alignment with the GAMRIF ToC and GAMRIF distinctiveness	Level One – Limited alignment with original GAMRIF ToC. There is no direct or indirect mention in the ToC. Level Two – Some alignment. Indirect mention in the ToC. Level Three – Good alignment. Direct mention in the ToC.
Criterion 3 – Neglected, underfunded and niche interventions	Areas that are neglected or/and underfunded based on evidence gathered	Level One – Not a neglected, underfunded or niche area (e.g. access to pneumococcal conjugate vaccine – lots of investment/work in this area/priority area for several funders/private companies) Level Two – An area that is to some extent neglected/underfunded - more investment could be provided to this area (e.g. vaccine adjuvant research) Level Three – Limited focus/investment/funding going to this area due to its complexity and other factors such as research in alternative management systems (integrated pesticide management systems) sanitation and WASH in farming/animal environments
Criterion 4 – Potential for high impact in LMICs	Potential for high, medium and low (direct) impact in LMICs, e.g., an area where capacity is already available, and it has a strong direct impact in the prevention of AMR in LMICs and that GAMRIF could contribute to.	Level One – An area that could have low impact in the prevention of AMR in LMICs (e.g., policy briefs developed in HICs that aren't directly applicable to LMIC contexts) Level Two – An area that could have medium impact in the prevention of AMR in LMICs (e.g., improve evidence base on the linkages between human and animal health to ensure learning from human vaccine development where not much work is currently being done and has potential to prevent/reduce AMR) Level Three – An area that could a high impact in the prevention of AMR in LMICs (e.g. increase uptake of existing vaccines with existing and/or additional fundings and uptake strategies).

Source: Own analysis, 2021

The six impact matrices for each of the thematic areas can be found below. For each matrix, we have provided an overview of the ranking given for the each of the potential AMR interventions identified in this gap analysis under each thematic area.

On diagnostics:

1. Continue to build the evidence base on the burden of AMR (for specific pathogens at regional and national level) to inform prioritisation of diagnostic tool R&D. This area is aligned with global AMR policy priorities (Criteria 1, green scoring). IHME, GLASS and Fleming Fund are active in this space, however more data needed. More data on the burden of fungal diseases and its resistance as well as diagnostics for falsified medicines. This area is more aligned with Fleming Fund's work (less with GAMRIF, red scoring for criterion 2), although GAMRIF could support diagnostic access (e.g., through market shaping) to synergise with Fleming Fund work. Interviewees and survey respondents mentioned more investment/funding could go into this area (Criterion 3, green scoring) and that this area could have a high impact in the prevention of AMR in LMICs (Criterion 4, green scoring)
2. Research utility/ use case/ potential role of diagnostics within the health care delivery system in LMICs. This area is aligned with (global and national) AMR policy priorities, however, more acknowledge might be needed according to interviewees (Criteria 1, green scoring). Late-stage translational R&D/operational research has not been GAMRIF's focus to date, but could be going forward, given the availability of credible delivery partners and high impact potential (Criterion 2, orange scoring). Interviewees and literature reviewed backed this area as very important to LMICs as well as an area that could be better funded (Criteria 3 and 4, green scoring).
3. Streamline/ harmonise regulatory and registration processes for new diagnostics. This is an emerging niche area that is not fully recognised in global AMR priorities (Criterion 1, orange scoring). It is an important area that can enhance the enabling environment for R&D on diagnostics. However, it is not necessarily fully aligned with GAMRIF ToC and might not be ODA compliant (Criterion 2, orange scoring). Interviewees, survey respondents and literature reviewed backed this are as very important to LMICs as well as an area that could be better funded (Criteria 3 and 4, green scoring).
4. Adapt/ repurpose or negotiate tiered pricing for existing diagnostic tools. Aligned with global AMR policy priorities, but more acknowledgement needed (Criteria 1, green scoring). As mentioned for AMR diagnostic intervention 2, late-stage translational R&D/operational research has not been GAMRIF's focus to date, but could be going forward, given the availability of credible delivery partners and high impact potential (Criterion 2, orange scoring). Interviewees and survey respondents backed this area as very important to LMICs as well as an area that could be better funded (Criteria 3 and 4, green scoring).
5. Build diagnostic clinical trial network capacity in countries with high AMR burden to reduce the cost and increase the speed of new diagnostic registrations. This is an emerging niche area that is not fully recognised in global AMR priorities (Criterion 1, orange scoring). As mentioned for AMR diagnostic intervention 2 and 4, late-stage translational R&D/operational research has not been GAMRIF's focus to date, but could be going forward, given the availability of credible delivery partners and high impact potential (Criterion 2, orange scoring). Interviewees and survey respondents backed this area as very important to LMICs as well as an area which would benefit even beyond the AMR space (Criteria 3 and 4, green scoring).
6. R&D for new LMIC-relevant diagnostic technologies to improve the existing pipeline. It is an area aligned with policy priorities and with GAMRIF ToC (Criteria 1 and 2, green scoring), and there are some specific gaps elaborated at WHO meetings (see Section 2.3.3). This area remains an important need, although interviewees voiced that many effective technologies already exist and where they do, the focus should be on increasing uptake (Criteria 3 and 4, green scoring).
7. Better coordination of R&D activities between diagnostics and therapeutics, towards co-introduction. There is a growing acceptance of the potential of this approach, see section 2.3.2 (Criterion 1, orange scoring). GAMRIF has indirectly been funding this area through its support to GARRD and FIND, however could extend the emphasis on this through influencing other partners (Criterion 2, green scoring). Interviewees and survey respondents backed this area as very important to LMICs as well as an area that could be better funded (Criteria 3 and 4, green scoring).

8. Fungal diagnostic R&D. This is an emerging niche that is not yet fully recognised in global AMR priorities (Criterion 1, orange scoring). Moreover, it has not been of GAMRIF's portfolio to date (Criterion 2, orange scoring). According to interviewees, there is a priority to carry out more R&D diagnostics work combined with improving access to existing antifungals and this is an area that is still being considered niche, and that could be better funded. (Criteria 3 and 4, green scoring).

Table 8: Impact Matrix - Diagnostics

Diagnostics	Criterion 1: Alignment with (global and national) AMR policy priorities and synergies with work of other AMR funders	Criterion 2: Alignment with the original GAMRIF ToC and GAMRIF distinctiveness	Criterion 3: Neglected, underfunded and niche interventions	Criterion 4: Potential for high impact in LMICs
1. Continue to build the evidence base on the burden of AMR (for specific pathogens at regional and national level) to inform prioritisation of diagnostic tool R&D				
2. Research utility/use case/potential role of diagnostics within the healthcare delivery system in LMICs				
3. Streamline/harmonise regulatory and registration processes for new diagnostics				
4. Adapt/repurpose or negotiate tiered pricing for existing diagnostic tools				
5. Build diagnostic clinical trial network capacity in countries with high AMR burden to reduce the cost and increase the speed of new diagnostic registrations				
6. R&D for new LMIC-relevant diagnostic technologies to improve the existing pipeline				
7. Better coordination of R&D activities between diagnostics and therapeutics, towards co-introduction				
8. Antifungal diagnostic R&D				

Source: Own analysis based on criteria described in Table 7

On therapeutics:

1. Continue to build the evidence base on the burden of AMR (for specific pathogens and at regional and national level) to inform prioritisation of therapeutic R&D. This area is aligned with global AMR policy priorities (Criteria 1, green scoring). IHME, GLASS and Fleming Fund are active in this space, however more data needed. More data on the burden of fungal diseases and its resistance as well as diagnostics for falsified medicines. This area is more aligned with Fleming Fund's work (less with GAMRIF, red scoring for criterion 2), although GAMRIF could support diagnostic access (e.g., through market shaping) to synergise with Fleming Fund work. Interviewees and survey respondents mentioned more investment/funding could go into this area (Criterion 3, green scoring) and that this area could have a high impact in the prevention of AMR in LMICs (Criterion 4, green scoring).
2. Invest in R&D for therapeutics that are in late-stage R&D - e.g., antibiotics for gonorrhoea. An area that is aligned with AMR policies and synergies and with the GAMRIF ToC (Criteria 1 and 2, green scoring). According to the literature reviewed, interviewees and survey respondents mentioned more investment/funding could go into this area (Criterion 3, green scoring) and that this area could have a high impact in the prevention of AMR in LMICs (Criterion 4, green scoring).
3. Invest in operational research to better understand the use case for Zoliflodacin in different health systems. An area that is aligned with AMR policies and synergies and with the GAMRIF ToC (Criteria 1 and 2, green scoring). According to the literature reviewed, interviewees and survey respondents mentioned more investment/funding could go into this area (Criterion 3, green scoring) and that this area could have a high impact in the prevention of AMR in LMICs (Criterion 4, green scoring).
4. Anti-fungal R&D. An area that is aligned with AMR policies and synergies (Criteria 1, green scoring), but not it is not yet covered in GAMRIF's current portfolio (Criterion 2, orange scoring). According to interviewees, there is a priority to carry out more R&D diagnostics work combined with improving access to existing antifungals and this is an area that could be better funded. (Criterion 3 and 4, green scoring).
5. Invest in late-stage R&D and/or market shaping to address access to existing antibiotics e.g., Paediatric indications, reformulation, voluntary licensing, demand side/use case research, price negotiation. An area that is aligned with AMR policies and synergies (Criteria 1, green scoring). Late-stage translational R&D/operational research/market shaping has not been GAMRIF's focus to date, but could be going forward, given the availability of credible delivery partners and high impact potential (Criterion 2, orange scoring). Interviewees and survey respondents backed this area as very important to LMICs as well as area that needs more investment/funding in the future (Criteria 3 and 4, green scoring).
6. Invest in regulatory science-research, to increase speed and reduce costs of regulatory approval for therapeutics. This is a niche emerging area that is not yet recognised in global AMR priorities and might not need to be covered specifically (Criterion 1, orange scoring). It is not fully aligned with GAMRIF ToC but might be important to improve enabling environment for all R&D activities linked to therapeutics. However, it might not be ODA compliant (Criterion 2, orange scoring). Interviewees and survey respondents considered this area as important to LMICs as well as area is quite nice and somewhat neglected (Criteria 3 and 4, green scoring).
7. Build therapeutic clinical trial network capacity in countries with high AMR burdens of disease, in order to reduce the cost and increase the speed of registration costs of new therapeutic registrations. This is a niche emerging area that is not yet recognised in global AMR priorities (Criterion 1, orange scoring). As area 6, it is not fully aligned with GAMRIF ToC but might be important to improve enabling environment for all R&D activities linked to therapeutics. However, it might not be ODA compliant (Criterion 2, orange scoring). Interviewees and survey respondents considered this area as important to LMICs and an area that needs more funding (Criteria 3 and 4, green scoring).
8. Invest in R&D of therapeutic alternatives such as phages and probiotics. An area that is aligned with AMR policies and synergies and with the GAMRIF ToC (Criteria 1 and 2, green). Literature reviewed, interviewees and survey respondents considered this area that is slightly neglected, and more investment would be needed (Criteria 3, green scoring). However, interviewees noted that this area is quite expensive, would require additional funds for clinical trials and lengthy regulatory pathways might be required which might not compensate for its potential impact on AMR (Criteria 4, orange scoring).

Table 9: Impact Matrix – Therapeutics

Therapeutics	Criterion 1: Alignment with (global and national) AMR policy priorities and synergies with work of other AMR funders	Criterion 2: Alignment with the original GAMRIF ToC and GAMRIF distinctiveness	Criterion 3: Neglected, underfunded and niche interventions	Criterion 4: Potential for high impact in LMICs
1. Continue to build the evidence base on the burden of AMR (for specific pathogens and at regional and national level) to inform prioritisation of therapeutic R&D				
2. Invest in R&D for therapeutics that are in late-stage R&D - e.g., antibiotics for gonorrhoeae				
3. Invest in operational research to better understand the use case for zoliflodacin in different health systems				
4. Antifungal therapeutic R&D				
5. Invest in late-stage R&D and/or market shaping to address access to existing antibiotics e.g. paediatric indications, reformulation, voluntary licensing, demand side/use case research, price negotiation				
6. Invest in regulatory science-research, to increase speed and reduce costs of regulatory approval for therapeutics				
7. Build therapeutic clinical trial network capacity in countries with high AMR burden, in order to reduce the cost and increase the speed of registration costs of new therapeutics				
8. Invest in R&D of alternatives to antibiotics, such as phages and probiotics				

Source: Own analysis based on criteria described in Table 7

On vaccines:

1. Operational research aimed at increasing uptake of existing vaccines. An area that is aligned with AMR policies and synergies and with the GAMRIF ToC (Criteria 1 and 2, green scoring). It is an area that was considered by interviewees and survey respondents as a very high priority area with high impact on AMR prevention in LMICs (Criteria 4, green scoring) However, interviewees highlighted that there is a need to invest further in this area (Criteria 3, orange scoring).
2. Early-stage research for potentially high-impact vaccines. An area that is aligned with AMR policies and synergies and with the GAMRIF ToC (Criteria 1 and 2, green scoring). Interviewees considered this area is underfunded (Criteria 3, orange scoring), which highlighted that way more investment is needed in early-stage research for high-impact pathogens with unclear R&D feasibility including *P. aeruginosa*, *S. aureus* and *E. coli* Moreover, there are pathogens – such as *Campylobacter spp*. and *H. pylori* – for which no products are in the pipelines and further research should be considered. It is an area that could have a high impact in the prevention of AMR in LMICs (Criterion 4, green scoring).
3. Adjuvant formulation research (adjuvants potential to reanimate and boost older/less successful vaccines while boosting immune system). Nor Adjuvant formulation research neither repurposing of vaccines is directly mentioned in AMR policy priorities, however vaccines development and improvement. Thus, it is mentioned indirectly (Criteria 1, orange scoring) and also covered indirectly in the GAMRIF's ToC (Criteria 2, orange scoring). According to interviewees, adjuvants formulation research is really important and impactful for LMIC - as new adjuvants may increase vaccine efficacy, particularly of protein-based vaccines. There are only a few laboratories in Africa researching the use of adjuvants in vaccine and interviewees highlighted that more research and support will be needed in this area (Criteria 3 and 4, green scoring).
4. Research into new methods to administer vaccines. Like adjuvants research, this area is not specifically mentioned in AMR policy documents reviewed but indirectly linked to vaccine development and improvements. Thus, it is mentioned indirectly (Criteria 1, orange scoring) and also covered indirectly in the GAMRIF's ToC (Criteria 2, orange scoring). It is a niche area, since 2018 the Vaccine Innovation Prioritisation Strategy (VIPS) group has been working on it (including the Vaccine microarray patches (MAPs)to release the vaccine through the dermis) but still further work and funding should go into the commercialisations of these technologies. Having easy to administer vaccines can really overcome some cultural barriers, fear of needles, and potential to be administered by a wider cadre of health care professionals. (Criteria 3 and 4, orange scoring).
5. Improve evidence base on the linkages between human and animal health to ensure learning from human vaccine development and vice versa. This area is not explicitly mentioned in policy documents (Criteria 1, red scoring). It is to an extent mentioned in GAMRIF's TOC as part of innovative solutions to AMR (Criteria 2, orange scoring). Interviewees and survey respondents considered this area to be a very niche area (Criteria 3, green scoring), but not as impactful as other interventions related to vaccine access and development (Criteria 4, orange scoring).
6. Research to develop more sophisticated methods to quantify AMR benefits of immunisation. This area is not directly mentioned in policy documents, nor in GAMRIF's ToC. However, policy documents mention the importance of immunisation and it is indirectly covered in the ToC under "general research activities" (Criteria 1 and 2, orange scoring). According to the reviewed literature, more sophisticated methods to measure cost-effectives of vaccines should be implemented and interviewees highlighted that understanding the benefits of immunisations is crucial to increase uptake and put an example the evidence gathered on the PVC vaccine. However, many did not consider having a high impact in LMICs compared to other areas (Criteria 3 and 4, orange scoring).
7. Repurposing of existing vaccines (e.g., mRNA vaccine). This area is not mentioned in policy documents, nor in GAMRIF's ToC (Criteria 1 and 2, red scoring). Interviews had mixed views on repurposing of existing vaccines, some believe that more emphasise should be given to repurposing some existing vaccines, for example the meningitis vaccines which has shown to have some protective effect against gonorrhoea, while others mentioned that more investment into innovative R&D should be the focus as there are still many pathogens with no products in the pipeline. This area might not have a high (direct) impact in the prevention of AMR in LMICs relative to other investment options (Criteria 3 and 4, orange scoring).

Table 10: Impact Matrix – Vaccines

Vaccines	Criterion 1: Alignment with (global and national) AMR policy priorities and synergies with work of other AMR funders	Criterion 2: Alignment with the original GAMRIF ToC and GAMRIF distinctiveness	Criterion 3: Neglected, underfunded and niche interventions	Criterion 4: Potential for high impact in LMICs
1. Operational research aimed at increasing uptake of existing vaccines (e.g,. Pneumococcal Conjugate Vaccine) in LMICs				
2. Early-stage research for potentially high-impact vaccines				
3. Adjuvant formulation research (adjuvants potential to reanimate and boost older/less successful vaccines)				
4. Research into new methods to administer vaccines				
5. Improve evidence base on the linkages between human and animal health to ensure learning from human vaccine development and vice versa				
6. Research to develop more sophisticated methods to quantify AMR benefits of immunisation				
7. Repurposing of existing vaccines (e.g., mRNA vaccine)				

Source: Own analysis based on criteria described in Table 7

On plants:

1. Producing more evidence on the volume of antimicrobials used as pesticides in crop protection and understanding their effect on human health. An area that is aligned with AMR policies and synergies and with the GAMRIF ToC (Criteria 1 and 2, green scoring). Interviewees and survey respondents considered this area as important to LMICs and an area that needs more funding (Criteria 3 and 4, green scoring).
2. R&D on alternative plant protection solutions (e.g., integrated pesticide management systems) suitable for use in LMICs. An area that is aligned with AMR policies and synergies and with the GAMRIF ToC (Criteria 1 and 2, green scoring). Interviewees and survey respondents considered this area as important to LMICs and an area that needs more funding (Criteria 3 and 4, green scoring).
3. Applying regulatory limits on use of antimicrobials in plants. This area is not specifically mentioned in AMR policy documents reviewed (Criteria 1, orange scoring), and it is not mentioned in GAMRIF's ToC (Criteria 2, red scoring). It is an area that is moderately neglected, and the potential impact due to challenges in applying to LMICs would need more cost-effectiveness/ feasibility studies to understand how limits can affect LMICs (Criteria 3 and 4, orange scoring).
4. R&D on innovative environmental diagnostic and monitoring tools (e.g., in farming to monitor AM concentrations in run-offs from pesticide use). This area is not specifically mentioned in AMR policy documents reviewed (Criteria 1, orange scoring), but mentioned in GAMRIF's ToC (Criteria 2, green scoring). Interviewees and survey respondents considered this area as important to LMICs and an area that needs more funding (Criteria 3 and 4, green scoring).
5. Improving surveillance on antimicrobial volumes/concentrations in the environment coming from pesticide use, at national level within LMICs as well as at global level. An area that is aligned with AMR policies and synergies (Criteria 1, green scoring) and indirectly with the GAMRIF ToC (Criteria 2, orange scoring). FAO platform has made some progress in this area, which means is an area that is not fully neglected and/or underfunded (Criteria 3, orange scoring). Interviewees mentioned this area might have high impact in LMICs, due to better understanding and having the ability to prevent outbreaks (Criteria 4, green scoring).
6. Operational research to understand how best to integrate existing mitigating solutions in current health/WASH programmes for farms to reduce the use of antimicrobials in crop plants. This area is not specifically mentioned in AMR policy documents reviewed (Criteria 1, orange scoring), but aligned with GAMRIF's ToC (Criteria 2, green scoring). Interviewees and survey respondents considered this area as important to LMICs and an area to explore further (Criteria 3 and 4, green scoring).
7. Reapplication or repurposing existing crop protection technology/innovation/research from other countries (i.e. from Europe or US). An area that is not aligned with AMR policies and synergies nor with the GAMRIF ToC (Criteria 1 and 2, red scoring). There are some challenges in transferring innovations/ interventions from HICs to LMICs, more needs to be done to adapt them well, however according to interviewees this area is not a high priority (Criteria 3 and 4, orange scoring).

Table 11: Impact Matrix – Plants

Plants	Criterion 1: Alignment with (global and national) AMR policy priorities & synergies with work of other AMR funders	Criterion 2: Alignment with the original GAMRIF ToC and GAMRIF distinctiveness	Criterion 3: Neglected, underfunded and niche interventions	Criterion 4: Potential for high impact in LMICs
1. Producing more evidence on the volume of antimicrobials used for crop protection as pesticides, and understanding their effect on human health				
2. R&D on alternative plant protection solutions (e.g., integrated pesticide management systems) suitable for use in LMICs				
3. Applying regulatory limits on use of antimicrobials in plants				
4. R&D on innovative environmental diagnostic and monitoring tools (e.g., in farming to monitor AM concentrations in run-offs from pesticide use)				
5. Improving surveillance on antimicrobial volumes/concentrations in the environment coming from pesticide use, at national level within LMICs as well as at global level				
6. Operational research to understand how best to integrate existing mitigating solutions in current health/WASH programmes for farms to reduce the use of antimicrobials in crop plants				
7. Reapplication or repurposing existing crop protection technology/innovation/research from other countries (i.e. from Europe or US)				

Source: Own analysis based on criteria described in Table 7

On environment:

1. Apply regulatory limits on 'acceptable levels' of pharmaceutical manufacturing discharges to reduce concentrations of antibiotics. This area is not specifically mentioned in AMR policy documents reviewed and not covered specifically in GAMRIF's ToC (Criteria 1 and 2, orange scoring). This area is very neglected, due to the challenges in applying these limits and the impact it could have on manufacturers is still unknown. There is a need cost-effectiveness and feasibility studies. According to interviewees, this is area which a potential high impact in LMICs (Criteria 3 and 4, green scoring).
2. Research to determine appropriate standardised measures for safe levels of manufacturing discharges and monitoring. This area is not specifically mentioned in AMR policy documents reviewed and not covered specifically in GAMRIF's ToC (Criteria 1 and 2, orange scoring). There is some progress in this area being carried out by AMR industry alliance, which published a paper on safe discharges. However, more needs to be done and there are some challenges of defining safe, high potential impact due to ability to measure and prevent outbreaks (Criteria 3 and 4, orange scoring).
3. R&D into LMIC-appropriate wastewater treatment solutions to reduce antibiotic concentrations in discharges. This area is not covered in AMR policy documents reviewed (Criteria 1, red scoring) and not covered specifically in GAMRIF's ToC (Criteria 2, orange scoring). Innovations exist in this area, but not applied in LMICs due to feasibility/ cost constraints. Evidence suggests that regular wastewater treatment are only partly effective, so more specialised solutions need to be applied for AMR –high impact (Criteria 3 and 4, green scoring).
4. Research to improve understanding of the scale of contamination and relative contribution of sources (agriculture, human/animal waste, manufacturing discharges). This area is covered in AMR policy documents reviewed (Criteria 1, green scoring) and not covered specifically in GAMRIF's ToC (Criteria 2, orange scoring). Interviews mentioned that research to improve understanding is as an important gap across all sources of evidence and can be very impactful (Criteria 3 and 4, green scoring).
5. Research to improve understanding of the effects of environmental contamination on human health. This area is covered in AMR policy documents reviewed (Criteria 1, green scoring) and not covered specifically in GAMRIF's ToC (Criteria 2, orange scoring). Interviews mentioned that research to improve understanding is as an important gap across all sources of evidence and can be very impactful (Criteria 3 and 4, green scoring).
6. Produce more evidence on the impacts of antibiotic use in agriculture and aquaculture including run-off into oceans and rivers. This area is covered in AMR policy documents reviewed (Criteria 1, green scoring) and not covered specifically in GAMRIF's ToC (Criteria 2, orange scoring). Literature reviewed, survey respondents and interviewees considered this area as important to LMICs and an area that needs more funding (Criteria 3 and 4, green scoring).

Table 12: Impact Matrix – Environmental

Environmental	Criterion 1: Alignment with (global and national) AMR policy priorities & synergies with work of other AMR funders	Criterion 2: Alignment with the original GAMRIF ToC and GAMRIF distinctiveness	Criterion 3: Neglected, underfunded and niche interventions	Criterion 4: Potential for high impact in LMICs
1. Apply regulatory limits on 'acceptable levels' of pharmaceutical manufacturing discharges to reduce concentrations of antibiotics				
2. Research to determine appropriate standardised measures for safe levels of manufacturing discharges and monitoring				
3. R&D into LMIC-appropriate wastewater treatment solutions to reduce antibiotic concentrations in discharges				
4. Research to improve understanding of the scale of contamination and relative contribution of sources (agriculture, human/animal waste, manufacturing discharges)				
5. Research to improve understanding of the effects of environmental contamination on human health				
6. Produce more evidence on the impacts of antibiotic use in agriculture and aquaculture including run-off into oceans and rivers				

Source: Own analysis based on criteria described in Table 7

On animals:

1. R&D on alternatives to antibiotics for animals and aquaculture. It is an area aligned with policy priorities and with GAMRIF ToC (Criteria 1 and 2, green scoring). According to interviewees, there are some investments on this area, however still an area that is neglected and underfunded strand of the one health approach (Criteria 3, orange scoring). Interviewees and survey respondents mentioned it is somewhat critical area for investment, that would be highly impactful given the high usage of antibiotics, poor sanctioning, regulation etc. (Criteria 4, orange scoring).
2. R&D on new animal vaccines. An area that is aligned with AMR policies and synergies (Criteria 1, green scoring) and indirectly with the GAMRIF ToC (Criteria 2, orange scoring). Some investments have gone onto this area, but more is needed. Evidence suggest it is a niche area and there is less interest within R&D community (Criteria 3, orange scoring). Interviews and survey respondents this could a critical area. Potential global rollout of animal vaccinations is seen as a key intervention towards to reducing impact of antibiotic over-use (Criteria 3, green scoring).
3. Increase uptake of existing vaccines for use in animals. An area that is aligned with AMR policies and synergies, and with the GAMRIF ToC (Criteria 1 and 2, green scoring). It is a neglected area with a need for focusing on increasing access, through further supply availability (Criteria 3, orange scoring). Interviewees mentioned the need for operational research to increase access to vaccines for humans and animals in agricultural communities – addressing the logistics and delivery capacity of vaccines. Given the scale of animal farming and current and projected growth in scale farming in LMIC, this would have a huge impact in preventing and managing the spread of AMR across animals and humans (Criteria 4, green scoring).
4. R&D for new, low cost, effective diagnostics tools and disease identification methods, to better guide appropriate antibiotic use. This area is not directly mentioned in policy documents, but they include a mention new, low cost and effective diagnostics in general (Criteria 1, orange scoring). It is aligned with GAMRIF's ToC (Criteria 2, green scoring). There are some investments in this area. However, according to interviewees, there is a need for more R&D innovations on low-cost diagnostics, to adapt existing ones and to develop new effective diagnostics technologies for the LMIC context (Criteria 3, orange scoring). Transforming diagnostics, detection capacity, information and knowledge sharing between farmers, laboratories, and animal health practitioners can have great benefits that would be wide reaching, for LMIC contexts and for uptake across animal farming and addressing several one health strands (Criteria 4, green scoring).
5. Improve data collection activities and data sharing practices (e.g., from farmer to lab). This area is not directly mentioned in policy documents (Criteria 1, orange scoring) and it is not covered by GAMRIF's ToC (Criteria 2, red scoring). Limited focus and investment going to this area due to the complex challenges of data collection and LMIC contextual factors (Criteria 3, orange scoring). According to interviewees, there is a need build existing capacity and investment from institutions and other key actors working in this space to improve data collection and inform more tailored interventions and R&D responses which might be quite impactful for LMICs (Criteria 4, orange scoring).
6. Improve coordination and facilitate knowledge sharing of best practices on animal health. An area that is aligned with AMR policies and synergies (Criteria 1, green scoring). It is indirectly covered by GAMRIF's ToC (Criteria 2, orange scoring). According to interviewees and survey responses, there is not enough resources being targeted for the coordination and knowledge sharing of best practices on animal health (Criteria 3, green scoring). Moreover, interviewees mentioned knowledge sharing of findings and products developed in HICs with LMICs stakeholders would have a high impact in the reduction of AMR in LMICs.
7. Local level research and pilot studies on farming practices/behaviours and decision making around animal husbandry, antibiotic use and antimicrobial detection, treatment and alternative practices. This area is not covered in AMR policy documents reviewed and not covered in GAMRIF's ToC (Criteria 1 and 2, red scoring). Limited focus/investment going to this area due to its complexity, however there is a strong need for local-level and more targeted research (Criteria 3, green scoring). More data would be needed to assess the impact of this area on AMR in LMICs, however interviewees mentioned this area is impactful (Criteria 4, orange scoring).
8. Research to better understand transference of antimicrobials from animal to environment, and then to humans. This area is not directly mentioned in policy documents, nor in GAMRIF's ToC (Criteria 1 and 2, orange scoring). Limited funding and focus in this area (Criteria 3, orange scoring), but if more funds are provided it might have an important impact in the prevention of AMR in LMICs. Research into transference has strong impact potential, spans

all the one health areas. Therefore, interviewees mentioned many would benefit from investing into this under-researched and under-resourced area (Criteria 4, green scoring).

Table 13: Impact Matrix – Animals

Animals	Criterion 1: Alignment with (global and national) AMR policy priorities & synergies with work of other AMR funders	Criterion 2: Alignment with the original GAMRIF ToC and GAMRIF distinctiveness	Criterion 3: Neglected, underfunded and niche interventions	Criterion 4: Potential for high impact in LMICs
1. R&D on alternatives to antibiotics for animals and aquaculture				
2. R&D on new animal and aquaculture vaccines				
3. Increase uptake of existing vaccines for use in animals				
4. R&D for new, low cost, effective diagnostics tools and disease identification methods, to better guide appropriate antibiotic use				
5. Improve data collection activities and data sharing practices (e.g., from farmer to lab)				
6. Improve coordination and facilitate knowledge sharing of best practices on animal health				
7. Local level research and pilot studies on farming practices/behaviours and decision making around animal husbandry, antibiotic use and antimicrobial detection, treatment and alternative practices				
8. Research to better understand transmission of antimicrobials from animal to environment, and then to humans				

Source: Own analysis based on criteria described in Table 7

4.0 Conclusions and observations

Based on Section 2 findings and the impact matrix analysis in Section 3, we have prepared a table that brings together the conclusions and the implications of those conclusions for possible actions and interventions GAMRIF might support.

Table 14: Conclusions and Observations

Conclusion 1: Significant evidence gaps exist across all study areas
Human health: The recent GRAM work improves the evidence base on AMR burden by pathogen and region, and the WHO PPL may need to be updated, since it includes only five of the seven pathogen-drug combinations that were found to cause the most deaths attributable to AMR. The GRAM data and analysis should also inform R&D reprioritisation and there will also be a need to translate the findings into location-specific policy decisions, including those relevant to IPC and access to essential antibiotics. There remains a need for better data on i) substandard/falsified medicines, mapping its correlation to AMR patterns, ii) better data on antifungal resistance and iii) the impact of vaccines on AMR. Despite relatively good intelligence on the status of technology candidates in the upstream R&D pipeline (albeit with scope for improvement), information is not as robust when it comes to i) understanding which existing technologies (diagnostics or therapeutics) could be adapted, or market shaped and ii) the framing/positioning and integration of new diagnostics and therapeutics within LMIC healthcare delivery systems, including economic utility. WHO diagnostic TPPs could be refined/nuanced, looking at what is needed for different syndromes and at different levels of the health system. **Environmental contamination:** More evidence needs to be generated to understand the relative contributions to environmental contamination from each source: agriculture, manufacturing discharges, human waste from consumption of antibiotics, and the mechanisms of transmission. **Plant health:** More evidence is needed on the volume of antimicrobials used for crop protection as pesticides and understanding their effect on human health. **Animal health:** There is incomplete, low quality and limited data on animal health (e.g., data on antimicrobial use and the human behaviour of farmers and veterinarians). Despite increased investment and volume of animal health data collection nationally, the numbers of sales to suggest usage are not conclusive.
Observations/possible actions
GAMRIF could support: the update of the WHO priority list based on the recent GRAM work; development of WHO TPPs nuanced for "use case"; technology pipeline[187] (through Product Development Partnerships (PDP) or Unitaid) both for early-stage R&D candidates as well as late-stage ones and/or existing medicines with a view to market shaping opportunities.
Conclusion 2: Need for operational research to reduce AMR and improve utility of R&D investments
Human health: More operational research is needed to understand the positioning and utility of diagnostics, therapeutics, and vaccines (e.g., uptake of existing vaccines) within LMIC health systems, including cost effectiveness modelling work. **Plant, environment and animal health**: More operational research on alternative plant protection solutions (e.g., integrated pesticide management systems) suitable for use in LMICs. Operational research is needed to understand context-specific farming management and biosecurity methods relevant to LMICs, particularly around current antimicrobial use. For animal health there remains the need for operational research into the LMIC context-specific tools for immediate, conclusive diagnostics and disease detection in animal husbandry and aquaculture contexts.

[187] WHO (2022): 2021 antibacterial agents in clinical and preclinical development: an overview and analysis

Observations/possible actions

The importance of operational research to reduce AMR and improve the utility of R&D investments was highlighted in interviwees and the survey. While some donors currently fund operational research in these areas, more resources should be targeted for operational research across all six study areas. GAMRIF could increase its emphasis on funding operational research in the future, and on the human health side, in particular on technology positioning and support to uptake of existing therapeutics/diagnostics technologies and vaccines. Use case/product introduction strategies could be prioritised for STI/gonorrhoea and sepsis/neonatal sepsis therapeutics and delivered through existing PDPs or market shaping specialist agencies.

On a national/regional level, GAMRIF could facilitate greater R&D evidence sharing into relevant transferable practice, knowledge, and intervention design. Investment could be made into collaborative partnerships, LMIC-based Research Centres, and digital evidence depository platforms. These collaborative activities could focus on facilitating between HICs and LMICs to build a strengthened evidence base for improved farming management, biosecurity practices and prudent antimicrobial use.

Conclusion 3: Gaps in regulation and compliance with regulation

Human Health: There is a need for regulatory science work, at international via the WHO - Prequalification of Medical Products and potentially though the European Medicines Agency, to streamline the product development pathway, including for antibiotic alternatives (e.g., phage and microbiome approaches). In diagnostics, there is a need for regulatory harmonisation to reduce the costs of conducting numerous field trials.

Plant, environment and animal health: There are still no international standards on reducing manufacturing discharges in wastewater. More research needs to be carried out on the cost of applying regulatory measures in LMICs for environmental contamination and animal health. Measures of sales of antimicrobials currently captured on international databases do not equate to accurate volumes and patterns of applied usage of antibiotic products, as our findings highlighted that high volumes continue to be manufactured illegally and distributed through unofficial channels. If regulation of compliance is absent, and if there are no viable alternatives or sufficient practitioner information and training, then non-compliance will continue.

Observations/possible actions

GAMRIF could support needs on regulation through the delivery partners it funds (e.g., CARB-X, GARDP, FIND). GAMRIF team could also support further research pieces looking at the regulatory harmonisation and streamlining of product development pathways for diagnostics and therapeutics and provide evidence to colleagues at DHSC that are involved/participated in meetings with international multilateral agencies such as the WHO.

There is a need for feasibility assessments and cost-benefit analyses of different applications. There may be potential for GAMRIF and the UK Government to use an influencing role with the AMR Industry Alliance and encourage collaborating governments (e.g., Argentina, China) to comply with reporting, for example, on antibiotic use in crops.

Improved regulation and compliance at a domestic level requires long-term investment, to be determined by a country's own volition and its capacity, with investment from HICs and multilateral agencies willing to provide leadership and guidance. GAMRIF's role could provide the partnership facilitation and regulatory support by funding ongoing research or new research on regulatory practices.

Conclusion 4: Need for better, global, and harmonised surveillance

Human health: There needs to be better access to diagnostics and better networking of diagnostic data within countries to enable surveillance and to better understand AMR burden of disease. Better surveillance can contribute

to more openly available data which can be used in future research and better data sharing across countries which is important for pandemic preparedness and preventing potential outbreaks.

Plant, environment and animal health: There is a significant lack of surveillance programmes in these areas. Moreover, evidence suggests that in many countries better data on diagnostics and therapeutics use is needed in order to improve surveillance. There is an overall need to produce better evidence.

Observations/possible actions

GAMRIF could support the access to available products and the development of new technology required for surveillance. It could synergise with the Fleming Fund's surveillance work, supporting R&D and enabling better access to existing diagnostics through market shaping initiatives (could be supported by a Unitaid call for proposals).

Conclusion 5: Need for R&D towards new technical solutions with relevance to LMIC settings

Human health: There continue to be innovation gaps when it comes to easy to use and affordable diagnostics for LMICs, novel therapeutics as well as new vaccines and ways of administering vaccines.

- Therapeutics: The priority need is for improved pipeline of candidates targeting Gram negative pathogens, e.g., *Salmonella* spp. and *Shigella* spp. as well as pathogens that have a serious health impact in LMICs, such as *S. typhi* and *A. baumannii*, which have hardly any promising drug candidates in the pipeline. Scientific challenges for antibacterials remain largely unresolved, e.g., getting compounds into hard-to-permeate Gram-negative bacteria and understanding under what circumstances clinically relevant resistance mutations arise.
- Diagnostics: Needs include POC test for sepsis, pneumonia and STIs; AST in key resistance categories; simpler diagnostics not requiring culture; binary test to determine if bacterial or not; and simple diagnostics to detect sub-standard/falsified medicines.
- Vaccines: Some novel technologies and approaches are being developed for new vaccines and their administration. Some of the novel technologies being used to develop new vaccines include: i) reverse vaccinology, ii) the use of novel adjuvants, iii) structural vaccinology and iv) bioconjugates and bacterial outer membrane vesicles (OMVs). OMV technology is being used to develop *N. gonorrhoeae* vaccines.[188] Moreover, evidence suggest that investigating the potential of mRNA vaccines (e.g., Covid 19 vaccine) and how these can make a difference for AMR is important. There is a need for further research to repurpose mRNA vaccines.

Observations/possible actions

This has been GAMRIF's traditional area of funding and there are continued innovation needs across the R&D value chain. The Global AMR R&D Hub's work has identified that more technology-related R&D needs to be done in LMICs in order to ensure local relevance and uptake. GAMRIF's ability to fund this type of work is crucial. GAMRIF could support this work though its existing PDP delivery partners or through new partnerships, e.g., through specific calls managed by Unitaid.

Through its existing delivery partners, GAMRIF could support possible expanded use of Artificial Intelligence (AI) in drug discovery, applying it to some of the pressing scientific challenges.

Conclusion 6: Need for improved AMR awareness

Plant, environment and animal health: Overall awareness around AMR has increased in recent years, however awareness is still low in terms of plant, environment and animal health. More awareness raising activities in collaboration with civil society organisations, research institutes and AMR funders could be supported in the future.

[188] Micoli, F., et al. (2021): The role of vaccines in combatting antimicrobial resistance

Observations/possible actions

GAMRIF could engage with other funders/donors/stakeholders as part of awareness-raising activities. Funding future studies on neglected areas related to plant and animal-related AMR (e.g., local level research and pilot studies on farming practices/behaviours around animal husbandry, antibiotic use and antimicrobial detection, treatment and alternative practices), and/or hosting engagement events with the broader AMR community would be a good way of raising awareness and sharing lessons learned from past studies funded through GAMRIF.

Conclusion 7: Need for late-stage R&D/market shaping to support introduction/scaling of improved technologies and access to existing tools

Human health: There are several opportunities for GAMRIF to support downstream commercialisation/market shaping as well as therapeutic and diagnostic field validation, commercialisation, and market entry work. This includes work on the demand side to better understand the use case and utility of new tools within LMIC healthcare settings, work with opinion leaders, procurement platforms, registration studies, training in technology use, and altering diagnostic and treatment algorithms. This also includes work on the supply side, to conduct a thorough R&D pipeline landscaping of candidate options which best meet LMIC needs, understanding costs and risks of suppliers, sharing demand forecasts with industry, supporting licensing deals to expand manufacturing supply, supporting studies to alter chemistry for reduced cost or improved shelf-life, supporting studies to field test and alter user interfaces for new diagnostics, and work to negotiate pricing.

Observations/possible actions

Specific opportunities for GAMRIF include:

There remains a significant barrier for LMICs to access existing treatments due to high pricing, lack of supply, few paediatric formulations and limited market shaping work to address these challenges. Through support to its existing delivery partners, GAMRIF could support the SECURE initiative or similar initiatives that emerge, as well as market shaping work to enable access to existing first-line antibiotics and support development of paediatric formulations for antibiotics.

- As appropriate diagnostic tests are already available for many fungal infections, the priority focus should be on expanding their use through market shaping and implementation science. GAMRIF could support through GAFFI, Unitaid, CHAI, DNDi, as they are working towards the same aims.
- FIND's STI diagnostic for gonorrhoea still needs regulatory, commercialisation, and market entry strategy investment and similarly GARDP's late-stage candidates will need late-stage R&D/market entry support. These needs could be supported through GAMRIF's existing partnerships with these organisations.
- Better landscaping of existing and near to market diagnostics in the pipeline which use artificial intelligence solutions to aid in diagnostic interpretation as well as clinical decision making – could be supported through FIND, if found to be prioritised in the scheme of other needs.
- Rapid low-cost kit to detect falsified medicines in late-stage development – could be supported through FIND or a Unitaid call.

Conclusion 8: Lack of funding especially in environment and animal health and need to increase LMIC relevance of human health R&D funding

Human health: Only 10% of total AMR R&D funding goes to LMIC-specific R&D and there is low activity in LMICs on technology specific R&D. A large portion of funding originates in HICs and remains in HICs. Consequently, more technology-related R&D needs to be done in LMICs for the benefit of LMICs.

Plant, environment and animal health: There is limited funding in research and interventions to prevent AMR, including funding for product development and innovation, to understand how the plant, environment and animal health is contributing to the prevalence of AMR in humans.

Observations/possible actions

GAMRIF needs to continue in its important role of addressing the gap of supporting more technology-related R&D in LMICs for the benefit of LMICs, to increase the LMIC relevance of tools.

GAMRIF needs to continue in its important role of addressing R&D in One Health dimensions outside of human health.

Conclusion 9: Need to integrate AMR solutions within broader health and WASH programmes

Human and plant, environment and animal health: There is a need to better understand the proportion of burden of disease that can be reduced by one or a combination of interventions and integrate AMR solutions/initiatives within broader health and WASH programmes and vice-versa. The OECD has worked on trying to compare the impact of different interventions on AMR – for example WASH programmes, or a combination of interventions – and in their latest work they have included vaccines. The OECD research only includes OECD countries, with a similar approach likely to be particularly useful for LMICs.

Observations/possible actions

GAMRIF could consider joining (either as a facilitator and/or funder) WASH-related R&D and innovation programmes and other horizontal health programmes to understand how these programmes are including AMR considerations. If the programmes are not including AMR considerations GAMRIF should propose that they do so.

Conclusion 10: Need for increased recognition of the role of socioeconomic factors in the current AMR landscape in LMICs

Human and plant, environment and animal health: Socioeconomic factors play an important role when other measures, such as regulation, are not in place and when the end-user can make use or dispose of antimicrobials freely (e.g., buying off-the-shelf to treat themselves, use of animal growth promoters, manufacturing discharges with no special WWTP treatment).

Observations/possible actions

Social and behaviour change communication interventions and raising awareness across the entire supply chain could be beneficial. Socioeconomic barriers need simultaneous attention alongside R&D, especially for applying operational and technical solutions. GAMRIF could provide much needed value through including these influencing factors in programming response. Socioeconomic analysis/research could be a requirement for obtaining GAMRIF support, R&D and innovations activities should consider the socioeconomic barriers and the economic impact of the products should be assessed alongside its social and potential to change behaviours.

Conclusion 11: Need for clinical trial network capacity strengthening

Human health: Clinical trial network capacity strengthening in countries with high AMR is needed to reduce cost and speed up the development of diagnostics, therapeutics, and vaccines in LMICs. There are several AMR funders contributing to this area. For example, GARDP is developing clinical trial network capacity specific to their therapeutic candidate zoliflodacin against drug-resistant gonorrhoeae. The Wellcome Trust's ADVANCE ID initiative has more potential to be a systemic clinical trials game changer but would also benefit the industry/private sector. As a result,

the initiative would indirectly benefit LMICs, although the intent is wider. In diagnostics, the Feasibility of Novel Diagnostics for TB in Endemic Countries (FEND-TB) clinical trial network for diagnostic R&D is reported to be the closest equivalent to GARDP's and Wellcome Trust's clinical trial initiatives, but this is in the initial stages of being developed.

Observations/possible actions

GAMRIF could meet clinical trial strengthening needs through the delivery partners it already supports. Moreover, GAMRIF could also support the dissemination/promotion of the existing clinical networks trials by given them more visibility at multilateral, ministerial meetings and other knowledge sharing activities that the GAMRIF team participates in.

Annexes

Annex 1 – Service Description

This Service Description is for delivery of a Gap Analysis to assess the current antimicrobial resistance (AMR) research and development (R&D) landscape and thereby identify underfunded areas in AMR research. The Gap Analysis is required to help the Global AMR Innovation Fund (GAMRIF), run by the Department of Health and Social Care (DHSC), make evidence-based funding decisions. DHSC is seeking an experienced Supplier to conduct the Gap Analysis and provide recommendations for future decision making.

Background

GAMRIF is part of the Global Health Security (GHS) Programme, within the International Directorate, at DHSC. It is a £50m Official Development Assistance (ODA) fund that supports early stage, innovative AMR R&D - in underinvested and neglected areas of AMR research – for the benefit of people in low- and middle-income countries (LMICs). The term R&D is used here to refer to tangible products (therapeutics, vaccines, diagnostics, etc.) as well as other innovations such as digital tools to aid clinical decision making, policy translation, or research to determine barriers to uptake of products and services, for example.

GAMRIF is a 'One Health' fund that invests in product development research across human, animal and environmental health. The fund supports high-quality research from around the world that has the potential to lead to tangible innovations that will help to prevent, detect and/or treat drug-resistant infections in resource-poor settings. GAMRIF's specific aims are to:

- establish international research partnerships and support research competitions that fund innovation and development of new technologies and interventions to tackle AMR
- leverage investment from other partners and donors to support sustainable financing in AMR R&D
- establish research partnerships using a 'One Health' approach
- fund projects that will develop solutions specifically for people in LMICs, where the burden of AMR is greatest

Through achieving these objectives, GAMRIF advances the aim of the GHS programme to prevent and reduce the future burden of AMR in LMICs, while also supporting improved disease detection and response.

More detail about GAMRIF can be found at www.gov.uk/government/groups/the-global-amr-innovation-fund

Based on the independent advice of an external 12-member Expert Advisory Board (EAB) and the former Chief Medical Officer for England, Prof. Dame Sally Davies back in 2017, GAMRIF has a mandate to target investments towards neglected and underinvested areas of AMR R&D. The high-level parameters also included focussing on drug-resistant bacteria; the WHO PPL for which new antibiotics are urgently needed (excluding TB); specific solutions to resistance rather than infection control; a portfolio of work packages rather than a single mechanism; and leveraging existing portfolios and delivery mechanisms where possible.

The GAMRIF Expert Advisory Board recommended that the following scientific and investment high-level criteria be used to scope the mandate of the Fund. These have remained GAMRIF's guiding principles during its first funding cycle.

Table 15: Scientific and Investment Criteria

Scientific Criteria	Investment Criteria
Topics must directly address the development, transmission and management of drug-resistant infections.	Work packages should complement not duplicate other UK Government projects, generating synergies where possible.
Individual projects must be directly and primarily relevant to needs of people in LMICs (i.e. ODA-eligible).	Projects should seek to leverage (or have the potential to leverage) funding from other international donors.
The scientific topics must focus on areas which have been neglected by other public and private funders.	Where possible, eligibility for funding should be as "global" as possible with investment made in the best research in the world, irrespective of location.
Projects must focus on innovation that creates meaningful new products or processes – this is not for iterative or duplicative research.	Separate work packages should target specific outcomes or "challenges" – rather than a single broad investigator-led competition.
The portfolio as a whole - and, where appropriate, individual work packages - should take a 'One Health' approach.	Where possible, funding should be available and accessible to underfunded researchers including SMEs and researchers in LMICs.

The AMR R&D funding landscape has moved on since the EAB guided GAMRIF to what was then considered 'neglected' or 'underfunded' areas of R&D that warranted investment. Therefore, DHSC wishes to procure a Supplier to conduct a Gap Analysis to assess the current AMR R&D landscape in the relation to LMIC needs.

The Task

The Supplier will conduct a Gap Analysis that addresses the following questions:

- What areas of AMR R&D that could most benefit LMICs are neglected and underfunded?
- In which areas of AMR R&D could future GAMRIF funds have the most impact?

The Supplier and GAMRIF will agree a list of sub-questions for the evaluation during the inception stage.

The Gap Analysis produced by the Supplier will be invaluable to guide possible GAMRIF funding decisions in the future, allowing us to make evidence-based decisions and remain in line with our original mandate. The Supplier will be expected to produce the following outputs.

Table 16: Expected Supplier Outputs and Timeline

Output	Timeline
Inception workshop to present workplan	Within two weeks of contract signature
Interim report and workshop	Two months after contract signature
Final report and workshop to present findings	Four months after contract signature

The contract will commence with a two-week inception phase, which will culminate in the inception workshop. The workplan presented will set out the project plan, the methodology and a risk register.

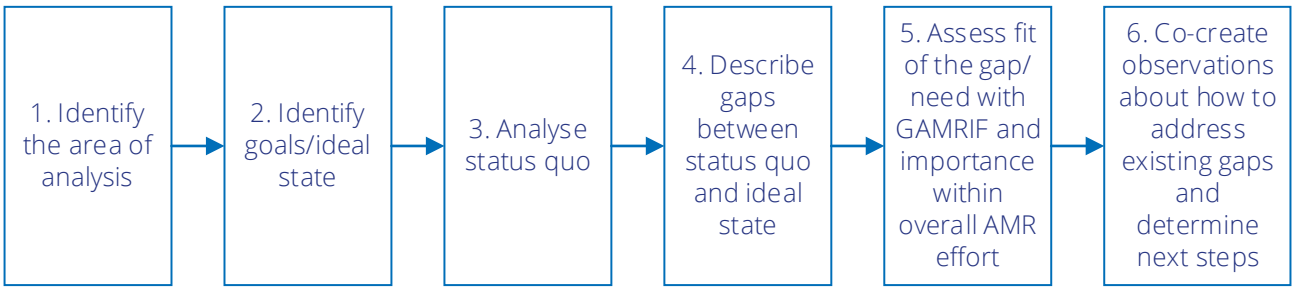
The final report should be no longer than 30 pages, excluding annexes, and include an executive summary. It must be suitable for publication and follow the DHSC style guide, paying particular attention to accessibility. The outline of the final report will be agreed between the Supplier and DHSC.

Annex 2 - Gap Analysis methodology and approach

Gap Analysis approach

Ecorys followed a six-step gap analysis approach for this study (Figure 3).

Figure 3: Gap analysis steps



Source: Own analysis, 2021

Step 1: Identify area of analysis

The study team carried out an initial review of the literature to prepare a list of 12 potential areas to be covered by the GAMRIF gap analysis study. At the Kick-off meeting, DHSC and the Ecorys team narrowed down the list of 12 potential scoping areas to the six included in Figure 1. The choices were informed by relevance to Low- and Middle-Income Countries (LMICs) and alignment with GAMRIF's aims and objectives.

Step 2: Identify ideal state

Through data analysis, discussion with the GAMRIF team, and the GAMRIF Theory of Change (ToC) (Figure 4), the team identified an ideal state in the AMR research landscape to compare it with the status quo in Steps 3 and 4.

Figure 4: GAMRIF Theory of Change

Input	Activities	Outputs	Outcomes	Impact
• Funding • GAMRIF Staff Capacity	• R&D projects funded to conduct innovative research across one-health approaches to AMR • Engagement & policy: Research projects funded in collaboration with international partners	• Encouragement of international partners to research innovative concepts tackling AMR in LMICs • High quality research that aims to: • Reduce the need for antibiotics through alternative medicines and vaccine development; Reduce use of antibiotics in farming of food producing animal; Reduce the environmental pollution of resistant bacteria and antibiotics; Improve the measurement of clinical data and its uptake into national level surveillance	• International focus and funding in tackling AMR in LMICs research increased • Innovative solutions tested and moved up TRL through the R&D Pipeline • Improved supply of appropriate and affordable products & tools for combatting AMR available to LMICs • Behaviour change in industry and clinical practice on LMICs from: research evidence into economic incentives and national policy; Food security evidence; Clinical practice pilot programmes	• Prevention and reduction of the likelihood of public health emergencies such as outbreaks and AMR • Early detection of threats in LMICs to save lives

Source: GAMRIF Theory of Change, 2021

Steps 3 and 4: Analysis of the status quo and describe gaps between status quo and ideal state

After data collection the team analysed the R&D landscape utilising an analytical framework (Annex 3) tailored to the gap analysis aims. Figure 5 provides an overview of the key questions included in the analytical framework, the detailed analytical framework in Annex 3 includes detailed questions tailored to the six study areas. By comparing the status quo and the ideal state identified in Step 2, the team was able to observe several gaps in the AMR R&D landscape in LMICs.

Figure 5: Analysis framework guiding questions

Assessment Categories	Assessment sub-category and broad assessment question
Evidence for decision-making	**Evidence base:** Is there a solid evidence base?
	Measure for success: Is there a clear measure for success?
Tangible products/results focused R&D (interventions)	**Intervention effectiveness and efficiency:** Is there a defined set of effective and efficient interventions? E.g. • What are the most effective initiatives/interventions? • What are the highest need new technologies for LMICs? • Which technologies could be adapted for improved LMIC utility? • Are there any technological challenges or opportunities? • Is there a sufficient business case/economic incentive? • Are there mechanisms for getting research into policy and practice (GRIPP) and are they used effectively? • What are the opportunities and constraints for access & uptake? • Are there additional barriers and enablers for the implementation of interventions? • Pros/cons of the existing mechanisms/architecture for managing coordinating and dispensing push and pull funds
R&D enabling environment	**Funding requirements:** Are funding requirements clearly specified and addressed?
	Regulatory: Are there regulatory challenges or opportunities?
	Awareness: Is there sufficient awareness to enable progress?

Source: Own analysis, 2021

Step 5: Assess the fit of the gaps with

A heat map (Section 3) was developed by the study team to rate key gaps identified in Step 3 and 4 against four criteria: i) Alignment with AMR policy priorities and work of other AMR funders, ii) Alignment with GAMRIF ToC and GAMRIF distinctiveness, iii) Neglected, underfunded and niche interventions and iv) Potential for high impact in LMICs.

Step 6: Co-create observations about how to address gaps identified

Section 4 provides a set of observations on key gaps that would require further investment and commitment by the AMR community to be addressed. This Section highlights which gaps could potentially be considered by the GAMRIF team in the preparation of GAMRIF 2.0 and were discussed with GAMRIF team at the final workshop.

Data collection activities

To inform the study, the team conducted a literature review, stakeholder interviews, and an expert survey.

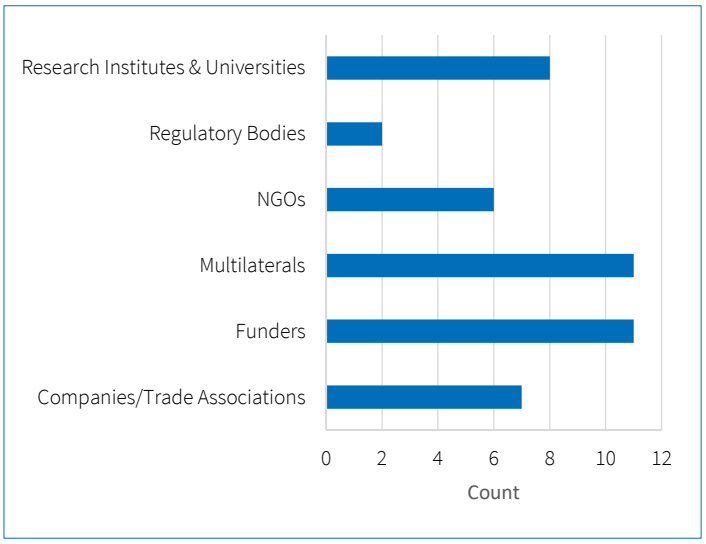
Key Literature Review: A review of key grey literature, peer-reviewed articles, and other documents recommended by key stakeholders allowed the team to answer questions around evidence gaps, enabling environment factors, priorities in the field, research enablers, and barriers. See an indicative list of documents reviewed in Annex 4.

Stakeholder interviews: During the inception phase, Ecorys worked with DHSC to develop an initial list of stakeholders. This comprehensive stakeholder list was the basis for setting up interviews. The initial list of stakeholders was expanded, where necessary, through snowball sampling. This ensured we covered the range of key stakeholders involved and relevant sectors (companies and trade associations, funders, multilaterals, NGOs, regulatory bodies, and research institutes and universities), to thereby gain a balanced perspective. The study team interviewed 45 experts through 36

interviews (nine held in groups, and 27 individually). Figure 6 shows a count of thematic areas discussed in each interview. A list of interviewee organisations is provided in Annex 5.

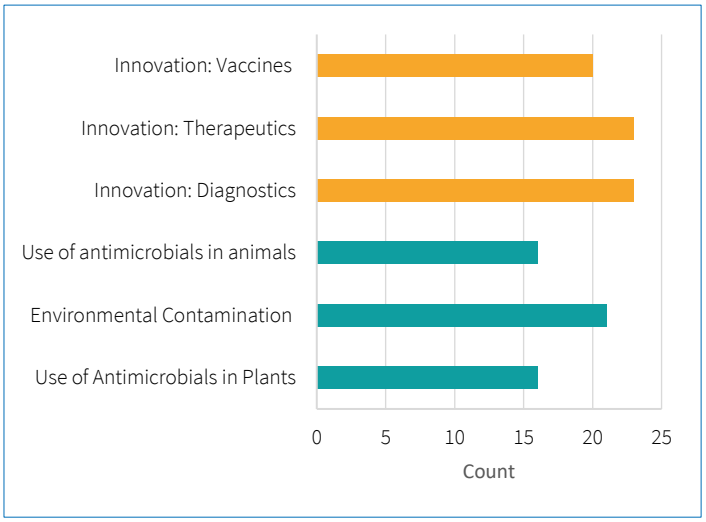
Expert survey: After developing initial findings, the study team developed a short expert survey to conduct a rapid assessment of expert opinions with regards to the identified research gaps. The survey was sent to over 170 AMR stakeholders and had an approximately 30% response rate, amounting to 55 responses.

Figure 6: Interviewees by Stakeholder Category



Source: Own analysis, 2021

Figure 7: Breakdown of topic areas discussed in interview



Source: Own analysis, 2021

Methodological limitations

Considering the exploratory nature and broad scope of this gap analysis study, it is important to note the following methodological limitations of this study.

The validity of survey responses. We sent the survey to stakeholders we knew to be active and engaged in AMR R&D and created a sample from a range of institutional types and geographic regions. We also asked survey respondents to rank their level of knowledge and experience on the six different areas, as a filter, so that they only responded to a set of

questions on those topics they were familiar with. However, we did not have control over who decided to respond to the survey. Thus, the survey responses may not fully capture heterogeneity within the AMR community or be representative of the target populations of interest such as established experts and/or beneficiaries of AMR interventions.

Staying in scope. Together with DHSC, we selected six areas for this study and excluded other relevant areas for AMR R&D, such as surveillance and WASH, that were thought to be less relevant for GAMRIF. However, some of the areas/topics outside of the scope are highly interlinked with areas in scope and many interviewees insisted that these are important areas for LMICs. Thus, some mention and reflections on areas out of scope are included in this report.

Resource limitations. This gap analysis inevitably had resource limitations (see Service Description in Annex 1), and it is therefore possible that the gaps captured are not exhaustive and some may have been missed.

Annex 3 – Analytical framework

Table 17: Analytical Framework

Analytical framework: human health dimensions				
	Assessment sub-category and broad assessment question	Area 1 –Diagnostic innovation (R&D and access)	Area 2 – Therapeutic innovation (R&D and access)	Area 3 – Vaccine and preventatives innovation (R&D and access)
Problem definition and solution space – LMIC focused	Scoping gaps: Understanding the problem context	▶ What are the well-known and less-know research areas of need within AMR R&D in relation to diagnostic innovation? ▶ What are the priority areas for LMICs in diagnostic innovation? ▶ Any LMIC country-specific examples?	▶ What are the well-known and less-know research areas of need within AMR R&D in relation to therapeutic innovation? ▶ What are the priority areas for LMICs in therapeutic innovation? ▶ Any LMIC country-specific examples?	▶ What are the well-known and less-know research areas of need within AMR R&D in relation to vaccines and preventative innovation? ▶ What are the priority areas for LMICs in vaccines and preventative innovation? ▶ Any LMIC country-specific examples?
	Goal identification and Future State: What is the ideal AMR state - particularly around early-stage R&D (GAMRIF)?	▶ What are the global AMR goals and ideal future state, particularly relate to human health dimensions? ▶ To what extent are these AMR goals realistic and relevant to the LMIC context? ▶ Are there other - additional or alternative ideas on what the global goals could include, or exclude, and alternative ideas of an 'ideal future state' in AMR?	▶ What are the global AMR goals and ideal future state, particularly relate to human health dimensions? ▶ To what extent are these AMR goals realistic and relevant to the LMIC context? ▶ Are there other - additional or alternative ideas on what the global goals could include, or exclude, and alternative ideas of an 'ideal future state' in AMR?	▶ What are the global AMR goals and ideal future state, particularly relate to human health dimensions? ▶ To what extent are these AMR goals realistic and relevant to the LMIC context? ▶ Are there other - additional or alternative ideas on what the global goals could include, or exclude, and alternative ideas of an 'ideal future state' in AMR?
	Evidence base: Is there a solid evidence base?	▶ What do we know/not know about AMR burden in LMICs, including related to specific pathogens, diseases, and patient types? (e.g., epi data through GLASS) ▶ Is there expert agreement on the relevance/importance of diagnostic innovation in addressing AMR in LMICs?	▶ What do we know/not know about AMR burden in LMICs, including related to specific pathogens, diseases, and patient types? (e.g., epi data through GLASS) ▶ What do we know/not know about R&D pipeline progress for AMR-relevant therapeutics and remaining gaps related to LMIC needs specifically? (e.g., pipeline tracking through Pew and WHO?)	▶ What progress has been made (and what more needs to be done) to improve the evidence for importance and potential impact of vaccines in AMR? (I.e., that increasing immunization will decrease the need for antimicrobials, hence reducing resistance)?

		▶ What do we know/not know about R&D pipeline progress for AMR-relevant diagnostics and remaining gaps related to LMIC needs specifically?	▶ Which further sources of data and/or experts should we consult to get more information on these questions? ▶ Possible role for GAMRIF/ODA funding?	▶ Is there any evidence to quantify the relationship - for example that x% vaccine coverage results in y% decrease in antimicrobial usage?
	Measure for success: Is there a clear measure for success?	▶ Is there expert agreement on the requirements for AMR-relevant diagnostics useful in LMICs (e.g., in terms of price, level of health system use, pathogen specificity, accuracy) ▶ What are the expert views on the potential/importance of co-introduction of new diagnostics with new therapeutics?	▶ Are there accepted criteria for what is needed re: Innovation in therapeutics for LMICs? e.g., accepted R&D finance amount, target pathogens/diseases/patient types, criteria for defining innovation, target # of therapeutics required over what time periods ▶ To what degree is there divergence versus similarity between therapeutic needs for LMICs versus HICs?	▶ Is there expert agreement/clarity on which AMR specific vaccines (covering which pathogens or diseases) would be most useful to reducing AMR in LMICs, e.g., identification of priority pathogens in humans and identification of key diseases?
	Intervention effectiveness and efficiency: Is there a defined set of effective and efficient interventions? E.g.: Are there any technological challenges or opportunities in the design? Is there a sufficient business case/economic incentive? Are there mechanisms for getting research into policy and practice (GRIPP) and are they used effectively? What are the opportunities and	▶ What are the pros/cons of the existing mechanisms/architecture for managing co-ordinating and dispensing push and pull funds for diagnostic R&D relevant to LMIC needs? ▶ What degree of focus is there on LMIC-specific needs (pathogens, diseases, animal versus human diagnostics)? ▶ What progress has there been to improve clinical trial effectiveness/efficiency for diagnostics and what more could be done? ▶ Are there any other non-traditional/niche/out of the box diagnostic technologies (e.g., AI assisted) on the horizon worth noting? Who is working on these? ▶ Possible role for GAMRIF/ODA funding?	▶ What are the pros/cons of the existing mechanisms/architecture for managing co-ordinating and dispensing push and pull funds for therapeutic R&D relevant to LMIC needs? ▶ What degree of focus is there on LMIC-specific pathogens, for example *H. pylori* or *Shigella* spp.? What progress has there been to improve clinical trial effectiveness/efficiency and what more could be done? ▶ What progress has been made with regard to stewardship and access of therapeutics and what more needs to be done? ▶ Are there any other non-traditional/niche/out of the box technologies on the horizon worth noting? Who is working on these? (e.g., artificial intelligence: For compound screening libraries – to look at potential hits for antibiotics; antifungal R&D; novel drug delivery systems compatible with LMIC healthcare settings) ▶ Possible role for GAMRIF/ODA funding?	▶ Which new vaccines (AMR-specific and AMR sensitive) are being developed to prevent drug-resistant infections (since 2019)? Are any of these being developed/tested in LMICs? ▶ Which existing vaccines could be improved for improved LMIC utility? Are there new vaccines that should be designed, to prevent against which infection disease/s and why? ▶ What are the opportunities and constraints for access and uptake of LMIC-relevant, AMR specific vaccines? ▶ Are there any innovative delivery systems for AMR sensitive or specific vaccines, which are compatible with low resource healthcare settings?

	constraints for access and uptake? Are there additional barriers and enablers for the implementation of interventions?			
Enabling environment – LMIC focused	**Funding requirements**: Are funding requirements clearly specified and addressed?	▶ In relation to LMIC diagnostic needs, which R&D pipeline stages/pathogens/diseases/patient pops are more/less well covered by existing funding? ▶ Possible role for GAMRIF/ODA funding?	▶ In relation to LMIC needs, which R&D pipeline stages/pathogens/diseases/patient pops and therapeutic technology types are more/less well covered by existing funding? ▶ Possible role for GAMRIF/ODA funding?	▶ In relation to LMIC needs, which R&D vaccines technology are more/less well covered by existing funding? ▶ Possible role for GAMRIF/ODA funding? ▶ Is the current funding going to the right places -i.e., most neglected/underfunded areas?
	Regulatory: Are there regulatory challenges or opportunities?	▶ What progress/challenges are there in relation to harmonisation and increased clarity of data required for diagnostic regulatory approval (to reduce registration cost and time to market)? ▶ What progress/challenges are there in relation to reimbursement plans e.g., to mandate use of diagnostics in certain cases or to cover costs of diagnostic use?	▶ What are the regulatory barriers and enablers in the development of therapeutics products of benefit to LMICs? e.g., progress on pathogen specific labels versus indication-driven approval ▶ What challenges/progress are there in relation to regulatory approval pathway for non-traditional therapeutics? ▶ Possible role for GAMRIF/ODA funding?	▶ What are the regulatory barriers and enablers in the development of vaccines of benefit to LMICs? ▶ Possible role for GAMRIF/ODA funding?
	Awareness: Is there sufficient awareness to enable progress?	▶ Is there sufficient awareness amongst the R&D community of the mechanisms to fund R&D and how to access these mechanisms? ▶ Is there sufficient awareness of LMIC-specific diagnostic R&D needs for diagnostic innovation?	▶ Is there sufficient awareness amongst the R&D community of the mechanisms to fund R&D and how to access these mechanisms? Is there sufficient awareness of LMIC-specific R&D needs for therapeutic innovation?	▶ Is there sufficient awareness amongst the R&D community of the mechanisms to fund R&D and how to access these mechanisms? Is there sufficient awareness of LMIC-specific R&D needs for vaccine innovation?
	Impact of funding existing gaps: Which AMR gaps would have most impact if provided with (additional) funding?	▶ What is the most critical gap that needs to be addressed in AMR that would have significant impact in its reach, effectiveness for advancing people/plant/animal health in LMIC? ▶ Any additional gaps in the enabling environment related that you believe GAMRIF should be focusing on?	▶ What is the most critical gap that needs to be addressed in AMR that would have significant impact in its reach, effectiveness for advancing people/plant/animal health in LMIC? ▶ Any additional gaps in the enabling environment related that you believe GAMRIF should be focusing on?	▶ What is the most critical gap that needs to be addressed in AMR that would have significant impact in its reach, effectiveness for advancing people/plant/animal health in LMIC?

		▶ Which areas of human health would GAMRIF funding have the most impact on? Which area, particularly of early-stage R&D would be recommended for GAMRIF to focus on?	▶ Which areas of human health would GAMRIF funding have the most impact on? Which area, particularly of early-stage R&D would be recommended for GAMRIF to focus on?	▶ Any additional gaps in the enabling environment related that you believe GAMRIF should be focusing on? ▶ Which areas of human health would GAMRIF funding have the most impact on? Which area, particularly of early-stage R&D would be recommended for GAMRIF to focus on?
Analytical framework – animal, plant and environmental dimensions				
	Assessment sub-category and broad assessment question	Area 4 –Use of antimicrobials in plants	Area 5 – Environmental contamination	Area 6 – Use of antimicrobials and AMR prevention in animals
Problem definition and solution space – LMIC focused	**Scoping gaps:** Understanding the problem context	▶ What are the well-known and less-know research areas of need within AMR R&D in relation to the use of antimicrobials in plants? ▶ What are the priority areas for LMICs in use of antimicrobials in plants? ▶ Any LMIC country-specific examples?	▶ What are the well-known and less-know research areas of need within AMR R&D in relation to environmental contamination? ▶ What are the priority areas for LMICs in environmental contamination? ▶ Any LMIC country-specific examples?	▶ What are the well-known and less-know research areas of need within AMR R&D in relation to use of antimicrobials and AMR prevention in animals? ▶ How much/what do we know about how beneficial/harmful for animal health is the use of antimicrobials in plants/environment? ▶ What are the uses of antimicrobials and AMR prevention in animals? ▶ Any LMIC country-specific examples?
	Goal identification and Future State: What is the ideal AMR state and particularly to early-stage R&D (GAMRIF)?	▶ What are the global AMR goals and ideal future state, particularly relate to animal, plant and environmental dimensions? ▶ To what extent are these AMR goals realistic and relevant to the LMIC context? ▶ Are there other - additional or alternative ideas on what the global goals could include, or exclude, and alternative ideas of an 'ideal future state' in AMR?	▶ What are the global AMR goals and ideal future state, particularly relate to animal, plant and environmental dimensions? ▶ To what extent are these AMR goals realistic and relevant to the LMIC context? ▶ Are there other - additional or alternative ideas on what the global goals could include, or exclude, and alternative ideas of an 'ideal future state' in AMR?	▶ What are the global AMR goals and ideal future state, particularly relate to animal, plant and environmental dimensions? ▶ To what extent are these AMR goals realistic and relevant to the LMIC context? ▶ Are there other - additional or alternative ideas on what the global goals could include, or exclude, and

				alternative ideas of an 'ideal future state' in AMR?
	Evidence base: Is there a solid evidence base?	▶ Is there any data on the overall use of antimicrobials in plants in LMICs? For example, crop production systems, human medicine include streptomycin and other aminoglycosides, tetracyclines, quinolones, and antifungals, horticulture. ▶ Is there any evidence of transmission risks from plants infected with resistant pathogens to humans? ▶ What is the magnitude of the available evidence? Any work to map use antibiotics patterns e.g., roses, citrus, rice cultivation esp. in suspected high-use countries like India, China?	▶ Is there a solid evidence base in the contribution of environmental systems to AMR in LMICs i) a transmission vector for human/animal associated resistant microbes; ii) as selective pressure for the development of resistance through complex mixtures of pollutants (e.g., antimicrobial concentrations in soil on crop farms or effluence from pharmaceutical factories); and iii) as a reservoir of novel genes)? ▶ Is there evidence/data on ecological factors that may encourage the development of resistance in various environmental systems and what concentrations are required to drive such resistance? ▶ Is there evidence of the human health impact of environmental contamination, especially scale of resistance development and variation among possible transfer pathways in LMICs? ▶ Is there evidence on harmful concentrations level, to enable target/limit setting? ▶ Are there any surveillance systems to monitor effluents in LMICs and any technology R&D needs around this? ▶ What is the magnitude of the available evidence	▶ Is there evidence of human drug resistant infection reduction from reducing antibiotic use in animals? ▶ What is the [magnitude] strength/of this evidence? ▶ Is there evidence of transmission risks from animals infected with [resistant pathogens] to humans? ▶ Is there expert agreement/clarity on which AMR specific livestock vaccines (covering which pathogens or diseases) would be most useful to reducing AMR in LMICs? ▶ What are the main challenges and issues within AMR R&D – with regards to Animal Health (aquatic and terrestrial) -issues known and being addressed? ▶ What are the lesser-known challenges and issues? Of these, which are specific to the LMIC context? ▶ What are the gaps in research findings and concrete evidence base and progress being made with regards to addressing these main challenges? ▶ Is there any data on the overall use of antimicrobials in animals (aquatic and terrestrial)? Is there any data for LMICs? ▶ What relevant data collection systems in place for measuring Animal Health and antibiotics use? ▶ Is there adequate (relevant, up to date) data available on conditions in animal husbandry systems and biosecurity n the LMIC context?

				▶ What progress would you say is happening in this area – for example, in terms of increased funding/resource mobilisation, awareness of issues globally, transmission of knowledge regionally and into practice? ▶ What relevant data collection systems in place for measuring Animal Health and antibiotics use on a national/international level? (and by whom?) What data is not being captured? (country, issue, political/sensitive areas)
	Measure for success: Is there a clear measure for success?	▶ Is there a clear measurement for plant health, the use of antimicrobials in plants and its effects in human health? ▶ To what extent is the use of antimicrobials in plants beneficial or harmful for human health? ▶ Extent of conversations in HIC versus LMICs on what would constitute responsible use (e.g., use of critical antibiotics e.g., EPA and citrus)	▶ How is environmental contamination including incidence, likelihood, scale of environmental system transmission to humans and impact measured? ▶ Is there sufficient evidence to enable setting of appropriate reduction targets (e.g., as part of the JPIAMR Environmental Dimensions of AMR conference output)? ▶ Is there any progress in setting pharma manufacture effluence standards?	▶ Is there a clear measurement for the effects of antimicrobials use in animals and its effects in human health? e.g., measure success through antibiotic volume reduction or through reduction in resistance.
	Intervention effectiveness and efficiency: Is there a defined set of effective and efficient interventions? E.g.: Are there any technological challenges or opportunities in the design? Is there a sufficient business case/economic	▶ Are there any effective initiatives/interventions that you are aware of related to plant health and the use of antimicrobials? ▶ Are there any promising technologies in development (either still in development or already available technologies which could be adapted or scaled) appropriate for reducing AMR stemming from plants in LMIC contexts? ▶ Have any interventions (e.g., bans/guidelines, alternatives to antibiotics) been designed/worked on in the last three years, particularly in LMICs? ▶ What are the barriers/enablers to ensure the use of antimicrobials in plants (for example, horticulture, human medicine production) contribute positively to human health?	▶ Are there any effective interventions that you are aware of related to the prevention of environmental contamination? e.g., voluntary action by parts of the pharmaceutical industry to limit the impact of antibiotic manufacturing effluence or technologies to remove antibiotics residue from aquatic or terrestrial reservoirs? ▶ Have any interventions (e.g., bans/guidelines, alternatives to antibiotics, incentives to ban or limit farm run-offs or LMIC factory effluence) been designed/worked on in the last three years, particularly in LMICs? ▶ What are the barriers/enablers to ensure the design of initiatives/interventions for the prevention of environmental contamination?	▶ Are there any effective interventions that you are aware of related to animal health and the use of antimicrobials? e.g., improved husbandry/aquaculture systems, better biosecurity practices and indirect reductions in antibiotics use, as championed by FAO/USAID in Bangladesh ▶ Are there any promising technologies in development (either still in development or already available technologies which could be adapted or scaled) appropriate for reducing AMR stemming from animals in LMIC

	incentive? Are there mechanisms for getting research into policy and practice (GRIPP) and are they used effectively? What are the opportunities and constraints for access & uptake? Are there additional barriers and enablers for the implementation of interventions?	▶ In what ways is the UK govt showing interest through DEFRA?	▶ Are there any promising technologies in development (either still in development or already available technologies which could be adapted or scaled) appropriate for reducing environmental contamination by point sources (factory, farm, hospital, community) in LMIC contexts? E.g., AMR sensitive wastewater treatment interventions e.g., around hospital run-off)	contexts? E.g., Fish vaccines and other solutions for aquaculture, use of alternative treatments, use of prebiotics and probiotics ▶ Effect of regulation/bans: Any success stories of removing medically important antibiotics from animal use? (e.g., colistin story pig farming in China) What is the capacity to enforce removal in LMICs? ▶ Have any interventions (e.g., bans/guidelines, alternatives to antibiotics) been designed/worked on in the last three years, particularly in LMICs? ▶ What are the barriers/enablers to ensure the use of antimicrobials in animals (e.g., husbandry, aquaculture) contribute positively to human health? ▶ How effective is interaction and resource/data sharing between research organisations to increase research efficiency?
Enabling environment – LMIC focused	**Funding requirements**: Are funding requirements clearly specified and addressed?	▶ Which organisations are funding research and intervention related to plant health and antimicrobials use in plants? ▶ Are there any R&D areas related to plant health that require further funding? ▶ Which areas related to plant health and its effects on human health are most impactful? e.g., Finding alternatives for antimicrobial prophylaxis and metaphylaxis in animals and plants.	▶ Which organisations are funding research and interventions related to the protection of environmental systems? ▶ Is there enough funding to work to fund existing interventions? ▶ Are there any main areas related to environmental contamination that require further funding? ▶ Which areas related to environmental contamination and its effects on human health are most impactful?	▶ Which organisations are funding research and intervention related to animal health and antimicrobials use in animals? ▶ Is there enough funding to fund existing interventions? ▶ Are there any main areas related to animal health that require further funding? ▶ Which areas related to animal health and its effects on human health are most impactful? e.g., Funding going to AMR in livestock issues, funding going to innovation in vaccines &

				antimicrobial options versus other types of innovation
	Regulatory: Are there regulatory challenges or opportunities?	▶ What are the legal/regulatory requirements for the use of antimicrobials in plants in LMICs (including in the horticulture, agriculture/crop production and production of human medicines)? Any country-specific examples? ▶ Are there any regulatory barriers/enablers in the use of antimicrobials in plants in LMICs? ▶ Setting of standards and guidelines on what would be responsible use levels as part of IPPC or voluntary agri-industry action? ▶ Any AMR sensitive coordination through international food standards harmonisation processes? E.g., Codex/Alimentarius Task Force on Antimicrobial Resistance in 2016? How broad is the engagement of national regulators with AMR following task force completion?	▶ What are the legal/regulatory requirements for to prevent the contribution of environmental systems to AMR in LMICs? Any country-specific examples? ▶ Are there any regulatory barriers/enablers in the contribution of environmental systems to AMR?	▶ What are the legal/regulatory requirements for the use of antimicrobials in animals in LMICs? Any country-specific examples? ▶ Are there any regulatory barriers/enablers in the use of antimicrobials in animals in LMICs?
	Awareness: Is there sufficient awareness to enable progress?	▶ Is there awareness around the use of antimicrobials in plants and effects on human health in LMICs? If yes, which stakeholders are aware? ▶ Which stakeholders should know about the use of antimicrobials in plants and effects on human health in LMICs that do not yet know? ▶ How can awareness among stakeholders (e.g., producers or purchasers of plant antimicrobials to contain AMR, regulatory bodies, civil society groups) linked to the use of antimicrobials in plants be improved?	▶ Is there awareness of the environment as a source of resistance in the wider AMR community? e.g., sources of pollution: Antibiotic residue from hospitals through sewages, farms, LMIC Gx and API pharma manufacturers and WWTPs) ▶ Which stakeholders should know about the contribution of environmental systems to AMR and its effects on human health in LMICs that do not yet know? ▶ How can awareness among stakeholders around environmental contamination be improved?	▶ Is there awareness around the use of antimicrobials in animals and effects on human health in LMICs? If yes, which stakeholders are aware? (e.g., farmers, veterinary professionals, consumers, policymakers ▶ Which stakeholders should know about the use of antimicrobials in animals and effects on human health in LMICs that do not yet know? ▶ How can awareness among stakeholders (e.g., farmers, veterinary professionals, consumers, policymakers) linked to the use of antimicrobials in animals be improved?
	Impact of funding existing gaps: Which AMR gaps would have most impact if	▶ What is the most critical gap that needs to be addressed in AMR that would have significant impact in its reach, effectiveness for advancing people/plant/animal health in LMICs?	▶ What is the most critical gap that needs to be addressed in AMR that would have significant impact in its reach, effectiveness for advancing people/plant/animal health in LMIC?	▶ What is the most critical gap that needs to be addressed in AMR that would have significant impact in its reach, effectiveness for advancing

	provided with (additional) funding?	▶ Any additional gaps in the enabling environment that you believe GAMRIF should be focusing on? ▶ Which areas of animal, plant and environmental health would GAMRIF funding have the most impact on? Which area, particularly of early-stage R&D would be recommended for GAMRIF to focus on?	▶ Any additional gaps in the enabling environment related that you believe GAMRIF should be focusing on? ▶ Which areas of animal, plant and environmental health would GAMRIF funding have the most impact on? Which area, particularly of early-stage R&D would be recommended for GAMRIF to focus on?	people/plant/animal health in LMIC? ▶ Any additional gaps in the enabling environment related that you believe GAMRIF should be focusing on? ▶ Which areas of animal, plant and environmental health would GAMRIF funding have the most impact on? Which area, particularly of early-stage R&D would be recommended for GAMRIF to focus on?

Annex 4 – Documents consulted

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WHO, WOAH, FAO (2021): Antimicrobial resistance and the United Nations sustainable development cooperation framework.

World Bank (2019): Pulling Together to Beat Superbugs: Knowledge and Implementation Gaps in Addressing Antimicrobial Resistance

Annex 5 – List of stakeholders consulted by organisation

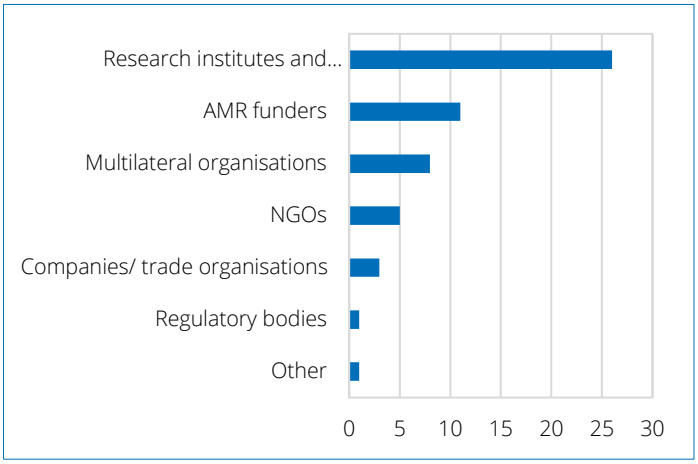
Table 18: Stakeholder List by Organisation

Organisation	Topics Discussed
Access to Medicine Foundation (AMF)	2, 3, 5
Afrigen Biologics	3
Animal and Plant Health Agency (APHA)	4, 5, 6
Bill and Melinda Gates Foundation (BMGF)	3
Center for Disease Dynamics, Economics & Policy (CDDEP)	1, 2, 3
Clinton Health Access Initiative (CHAI)	1, 2
FIND	1
Fleming Fund	1, 2, 3, 4, 5
Food and Agriculture Organization (FAO)	4, 5, 6
Global Action Fund for Fungal Infections (GAFFI)	1, 2, 3, 4
Global AMR R&D Hub	1, 2, 3, 4, 5, 6
GSK (GlaxoSmithKline)	3, 5
HealthforAnimals	6
Hileman Laboratories	1, 2, 3
Innovate UK (UKRI)	1, 2
International Development Research Centre (IDRC)	4, 5, 6
Janssen	2
Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)	5
London School of Hygiene & Tropical Medicine	1, 2, 3, 4, 5, 6
Medical Research Council (MRC - UKRI)	1, 2, 3
National Environmental Research Council (NERC – UKRI)	4, 5
Oxford Big Data Institute (BDI)	1, 2, 5
ReAct (Europe, North America)	1, 2, 3, 4, 5, 6
The International Centre for Antimicrobial Resistance Solutions (ICARS)	6
Unitaid	1, 2
University of KwaZulu-Natal (UKZN)	1, 2, 3, 4, 5, 6
Wellcome Trust	1, 2
World Health Organisation (WHO)	1, 3, 4, 5, 6
World Organisation for Animal Health (WOAH)	5, 6

Legend: 1. Innovation: Diagnostics; 2. Innovation: Therapeutics; 3. Innovation: Vaccines (development and access); 4. Use of antimicrobials in plants 5. Environmental contamination; 6. Use of antimicrobials in animals "

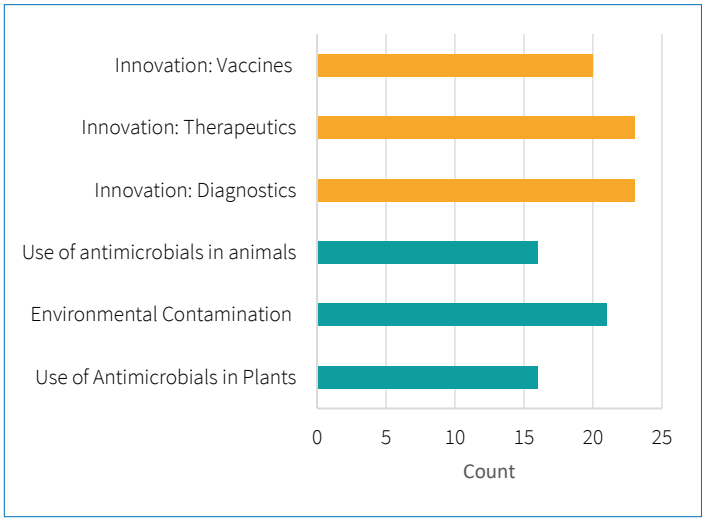
Annex 6 - Overview of survey responses

Figure 8: Expert Survey Respondents by type of organisation



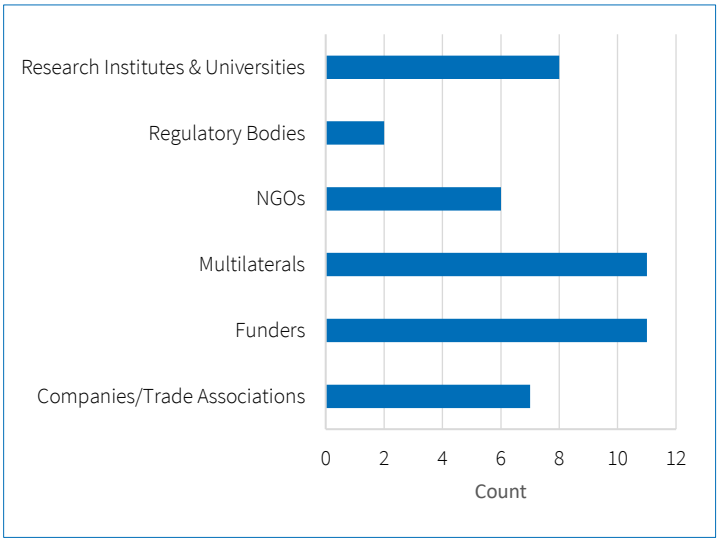
Source: GAMRIF gap analysis survey

Figure 9: Breakdown of topic areas discussed in interview



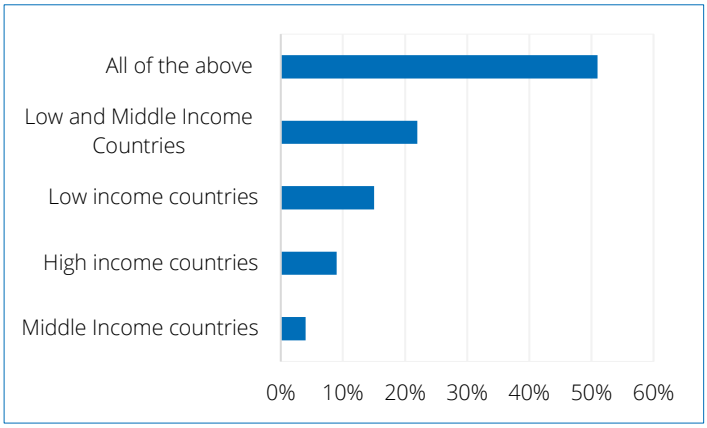
Source: GAMRIF gap analysis survey

Figure 10: Interviewees by Stakeholder Category



Source: GAMRIF gap analysis survey

Figure 11: Expert survey respondents by area of focus in AM



Source: GAMRIF gap analysis survey

Annex 7 – Full Vaccine Table

Table 19: List of Vaccines

Pathogen	Priority level[189]	Current vaccines pipeline	Feasibility for vaccine development	Possible interventions
A. baumannii	1	No candidates in clinical trials and no past candidates either	Low – due to biological and clinical development challenges	Investing in early-stage and preclinical programmes targeting *A. baumannii* Currently only Cefiderocol (antibiotic) has a project targeting several MDR gram-negative pathogens including *A. baumannii*
P. aeruginosa	1	No candidates in clinical trials but previous inactive clinical trials	Low – due to biological and clinical development challenges	Preclinical research (e.g., antigen discovery & selection, animal models) but also explore alternatives (e.g., monoclonals) and better understand burden/epidemiology/transmission Johnson & Johnsonand Pfizer have discovery and preclinical projects to develop an antibody against *P. aeruginosa*
Enterobacteriaceae (family)	1	Three vaccine candidates in early stage.	Low – due to biological and clinical development challenges	Collect data and explore alternatives (e.g., monoclonals) Johnson & Johnson's *E. coli* vaccine (ExPEC9V) could protect against more Enterobacteriaceae family pathogens beyond *E. coli*. This vaccine is current in Phase III
K. pneumoniae	1	There is no current vaccine for *K. pneumoniae*, and the pipeline is comprised of three preclinical candidates.	Medium – feasible but very challenging.	Explore alternatives (e.g., monoclonals), collect data to understand better the burden of disease, feasibility of vaccines development and implementation and lastly likelihood of introducing vaccines in hospital settings (e.g., couples of weeks before surgery).

[189] Based on WHO priority list: Priority 1: Critical, Priority 2: High and Priority 3: Medium

E. coli (enteric)	1	One vaccine candidate in Phase III	The high antigenic diversity of *E. coli* (enteric) is a challenge for vaccine development, but inclusion of LT toxoid and fimbrial antigens in a potential vaccine may help cover 70-80% of strains.	Accelerate clinical development. Johnson & Johnson's *E. coli* vaccine (ExPEC9V)
Enterobacter spp.	1	No candidates in clinical trials and no past candidates either	Low – due to biological and clinical development challenges	Collect data and explore alternatives (e.g., monoclonals)
Serratia spp.	1	No candidates in clinical trials and no past candidates either	Low – due to biological and clinical development challenges	Collect data and explore alternatives (e.g., monoclonals)
Proteus spp.	1	No candidates in clinical trials and no past candidates either	Low – due to biological and clinical development challenges	Collect data and explore alternatives (e.g., monoclonals)
Providencia spp. (Enterobacteriaceae family)	1	No candidates but ongoing research on possible vaccines using	Low – due to biological and clinical development challenges	Collect data to understand better the burden of disease and feasibility of vaccines development and implementation

		Immunoinformatics Approach[190]		
C. difficile	1	No vaccines against *C. difficile* are available on the market. Vaccines that target the major pathogenic factors toxin A and toxin B (TcdA and TcdB, respectively) are in clinical development.	Low – due to biological and clinical development challenges	Collect data to understand better the burden of disease and feasibility of vaccines development and implementation Sanofi started a phase III clinical trial in individuals (>50 years) who are at risk of *C. difficile* infection to assess the efficacy to prevent primary symptomatic episodes.
E. faecium (Enterobacteriaceae)	2	Three vaccine candidates in early stage.	Low – due to biological and clinical development challenges	Collect data and explore alternatives (e.g., monoclonals) Johnson & Johnson's *E. coli* vaccine (ExPEC9V) could protect against more Enterobacteriaceae family pathogens beyond *E. coli*. This vaccine is current in Phase III
S. aureus	2	Three vaccines in clinal trials	Low – due to biological and clinical development challenges	Continue to invest in promising vaccine candidates such as the virulence factor SpA and the pore-forming toxins leukocidins as well as novel adjuvants that stimulate cell-mediated immunity and increase vaccine efficacy have been identified and are in the preclinical phase of development. Johnson & Johnson has a vaccine candidate against *S. aureus* in preclinical stage. Pfizer advanced its four-component vaccine candidate SA4ag (containing CP5, CP8 and the two surface protein antigens ClfA and MntC) to a phase IIb trial. However, trial was discontinued due to a low statistical probability for the study to meet the predefined primary efficacy end points.
H. pylori	2	No active clinical developments but there have been previous investments	Low – due to biological and clinical	Collect data and explore alternatives (e.g., monoclonals) Private companies could engage in in-house R&D, through acquisition or collaboration with other companies, or by joining existing public private partnerships, to target resistant pathogens for which R&D is limited, such as *Campylobacter* spp. and *H. pylori*.

[190] Designing a Recombinant Vaccine against *Providencia* rettgeri Using Immunoinformatics Approach

		to develop a vaccine which have failed.	development challenges	
Campylobacter spp.	2	No active clinical developments	Low – due to biological and clinical development challenges	Private companies could engage in in-house R&D, through acquisition or collaboration with other companies, or by joining existing public private partnerships, to target resistant pathogens for which R&D is limited, such as *Campylobacter* spp. and *H. pylori*.
Salmonella spp.	2	Three vaccines in early stage of development.	Low – due to biological and clinical development challenges	Continue to fund discovery/preclinical projects targeting *Salmonella* spp.
N. gonorrhoeae	2	One vaccine in phase III development.	Medium – Feasible but very challenging.	Develop and fund vaccination programmes in LMICs. The *N. gonorrhoeae* vaccine is due to market in 2023/2024. The case for development of a vaccine targeting *N. gonorrhoeae* has been strong due to high incidence, high morbidity, and circulation of resistant strains.
S. pneumoniae	3	A total of four vaccines are in development. One in preclinical trial, one vaccine in Phase II, another one in Phase III and one approved (Vaxneuvance™)	High feasibility	Continue to improve existing vaccines and invest in the roll-out and take-up of vaccines.
Haemophilius influenzae	3	No vaccine under development. One vaccine recently approved Shan6™ [Sanofi]	High feasibility	Continue to improve existing vaccines and invest in the roll-out and take-up of vaccines.
S. typhi	3	There are 20 marketed vaccines against *S. typhi*, and	High feasibility	Continue to improve existing vaccines and invest in the roll-out and take-up of vaccines.

		many others are in development.		
Shigella spp.	3	No vaccine is currently widely available against Shigella but pipeline includes a moderate number of candidates, a few of which are currently in phase I and phase II trials.	High feasibility	Clinical development for Shigella should be accelerated, testing promising vaccine candidates in the target population as quickly as possible.

Source: Author's analysis based on information gathered via interviews and three publications: i) Access to Medicine Foundation (2021): Antimicrobial Resistance Benchmark 2021 ii) Antimicrobial Resistance Collaborators (2022): Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis; iii) Wellcome and Boston Consulting Group (2018): Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities