



UNDERSTANDING CROSS-
FUNCTIONAL RELATIONS IN
THE MANAGEMENT OF
ANTIMICROBIAL RESISTANCE



MARCH 18, 2023

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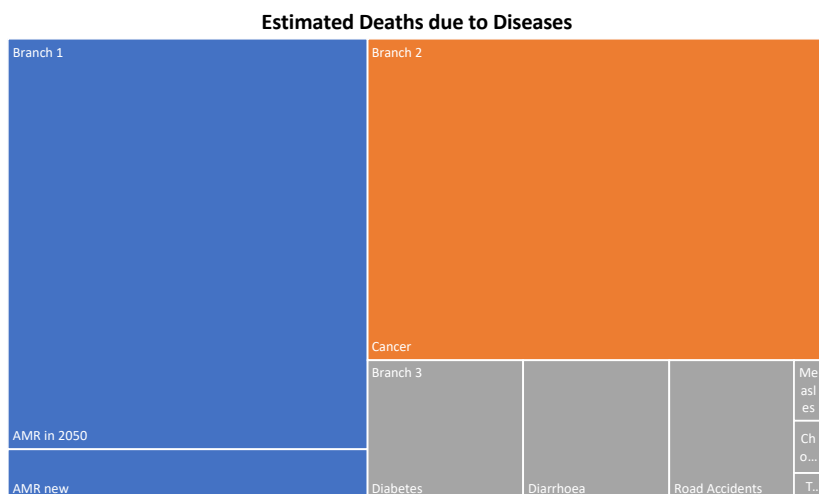
Section 1: System analysis

According to the WHO Director-General, Dr Tedros Adhanom Ghebreyesus, “Anti-microbial resistance (AMR) undermines modern medicine and puts millions of lives at risk” (WHO, 09 December 2022). The (GLASS Report, WHO 2022) document an increase of 15% in AMR rates in the COVID era (2020) as compared to 2017.

Problem Statement

AMR is a global problem which is expected to cause 10 million deaths by 2050. It impacts multiple industries (such as healthcare, agriculture, animal farming and the environment) and multiple actors (such as doctors, patients, caregivers, farmers, poultry farmers, etc.). With evidence linking high mortality and morbidity of infectious diseases AMR, there is a need to rationalize antibiotics (antiBs) use globally.

According to (Murray et al., 2022), an estimated 4.95 million deaths in 2019 were associated with bacterial AMR including 1.27 million deaths attributable to bacterial AMR. Globally, 189,000 YLLs (years of life lost) and 192,000 DALYs (disability-adjusted life years) were reported. Developing and under-developed healthcare systems, such as South Asia and Sub-Saharan Africa, reported a higher than average on these parameters. As per a UNEP (*Antimicrobial Resistance: A Global Threat, 2022*) and Murray et al., AMR will lead to about 10 million deaths annually by 2050. Over the next 10 years, AMR can cost US\$ 3.4 trillion of



Source: UNEP 2023, O'Neill 2016, Murray et al., 2022

the global GDP and push 24 million more people into extreme poverty.

The Guiding Star: With this study, the author intends to propose

interventions to restrict AMR-linked mortality to ~3 million per year by 2050 [Appendix C].

The **near star** is to create a multi-sectoral and regional collaboration to reduce antiB use by at least 30% in the next 5 years.

Stakeholders, trends, underlying structures & causal loops

AMR is a problem for many industries and stakeholders.

Deep structure of AMR [Appendix A]: As resistance for first-line antibiotics (antiB) develops, the use of broad-spectrum antiBs (carbapenems etc.) will grow and will lead to multidrug resistance (MDR) infections and thereby, increased mortality and morbidity. In 2022, the CTAs (countries, territories, and areas) reported >8% of bloodstream infections caused by carbapenem-resistant pathogens. WHO reported a global spread of carbapenemase-producing Enterobacterales and high rates of carbapenem and aminoglycoside resistance in *Acinetobacter* spp. ($\geq 56\%$). Other factors (healthcare coverage, accessibility, treatment costs, awareness, etc.), actors (pharma, doctors, policymakers, farmers, etc.) and drivers (local and global) also have a significant contribution to this pandemic [Appendix D, E and F].

At the ‘micro-level’ [Appendix D], lack of awareness, limited decision-making power, socio-economic and literacy variance, and demand for cheaper products (drugs and food) lead to limited power, moderate interest, and a high impact on driving AMR.

At the meso-level, power to influence and interest varies significantly. For instance, pharma has high power but low interest largely due to expected ROI and difficulties associated with developing new-generation antibiotics. On the contrary, providers have high interest but moderate power. Many of the prescribers do not have access to stewardship programs and diagnostic tools and must consider the cost of care to the patient before making a treatment decision [R1, R5, B2 Appendix F]. Farmers and poultry owners have no interest and less power and use antibiotics irrationally to ensure a cost-effective yield [R7, Appendix F].

However, interventions at the meso-level can yield a high impact on the incidence and emergence of AMR since most of the stakeholders at this level have decision-making power.

Pharma has high power and low interest [Appendix D]:

Despite yielding high power and plausible impact, the unwillingness of pharmaceutical companies to develop new-age antibiotics (Appendix D) is largely driven by the limited perceived ROI of antiB development, emergence of other profitable therapeutic areas or TAs (such as cancer) and extensive price controls exercised by many healthcare systems globally (B1 Appendix F). According to the (WHO, 2022), a total of 46 of the 80 clinical development projects evaluate traditional antibiotics and overall, only 49 clinical development projects target priority pathogens. Despite the reduced effectiveness of current antiBs (Thomas & Wessel, 2022), the investment and the interest of pharma have remained substantially low (over the last 10 years, VC funding to antiB-focused firms was just \$1.6 bn compared to \$26.5 bn to cancer drug developers) leading to a substantial drop in NCE pipeline (clinical trial initiation for antiB NCE declined by 33% during 2016-2020 as compared to 2011-2015). [Ref: Appendix E and F].

The downstream effect of inaction or limited interest of pharma in AMR has resulted in limited NCE development for infections and thereby, increasing dependence on the currently available antiB arsenal for which drug resistance has led to reduced efficacy. Further, since most of the NCE antiBs (80%+ as per (Thomas & Wessel, 2022)) are being developed by smaller companies, the sustenance of related trials may be challenged and the dependence on public-funded support may grow.

Providers have high interest but moderate power [Appendix D]:

Multiple actors misuse antiBs for different reasons, however, providers are central to the rise of AMR. According to the CDC (*CDC: 1 in 3 Antibiotic Prescriptions Unnecessary | CDC Online Newsroom | CDC*, 2016), at least 30% (~47 million) of the antibiotics prescribed in the

US may not be needed at all. Much of this overprescription/overuse of antiBs is driven by either lack of knowledge and support (steward programs) to prescribing HCPs and/or patient's pursuit to recover quickly {Appendix E and F}. GPs have been the largest prescribers of antiBs across healthcare systems, however, do not have access to relevant diagnostic tools and related stewardship programs to manage drug-resistant infections. Further, they have been reluctant to share information with other stakeholders. According to (Zgliczyński et al., 2022), in a survey of 504 **medical doctors**, only 47% of the respondents were aware that the use of antiBs as growth stimulant on livestock was illegal in the EU. Nearly 65.28% of the respondents did not have access to appropriate materials on AMR counselling and ~92.5% never or rarely shared resources on prudent antiB use. Unsolicited antiB rotation, attempt to make recovery quicker, lobbying by pharma and patient influence too play a critical influencing role in GP's use of antiBs.

This leads to the emergence of MDR (multi-drug resistive), untreatable infections and entry of these pathogens into the food chain. Many clinical practices are being forced to increase the use of broad-spectrum antibiotics early in the infection cycle, sometimes even for viral infections (especially in respiratory tract viral infections), to ensure recovery [B2, Appendix F]. This has further led to an increase in difficult-to-treat MDR infections and related economic burden.

Consumers have low power and moderate interest

Patient-related factors (self-medication, low compliance and adherence) augment the issue of AMR. According to (Green et al., 2023), driven by inconvenience due to healthcare systems, financial barriers, and unregulated access to antiBs in LMICs, there was a substantial increase in self-medication and low adherence to prescribed antibiotics. In a systemic review by (Xu et al., 2019), the pooled surveillance of self-medication with antibiotics (SMA) was about 46% among university students. Among LMICs, the prevalence of SMA varied from 11.1%

(Brazil) to 90.7% (Congo). Factors, such as low literacy rates and awareness, easy access to cheaper generic (Gx) versions, and social insensitivity towards the cost (profit/cost saving is more critical), are known to drive such behaviours.

Further, consumer callousness and government failure to improve living conditions have led to water pollution and transmission of AMR. In regions with higher population density, the incidence of communicable infections is high, which has led to repeat infections and increased AMR. Across studies (Alividza et al., 2018; Barah & Gonçalves, 2010; Planta, 2007), the role of other socio-economic factors, such as poverty and awareness, in the spread of AMR has been implicated. Especially in LMICs, there is increased evidence of poor hygienic conditions and key systemic issues, such as open defecation. Through water contamination and sewage mismanagement, drug resistance has entered portable and irrigation water and has a direct impact on agriculture and marine industry, contributing to cross-border AMR [R6, Appendix F]. According to (Bürgmann et al., 2018), understanding the fate of AMR pathogens and antibiotic resistance genes (ARGs) through the lens of water sanitation and hygiene practices is critical to control the spread of AMR through irrigation and potable water.

Regulators and policymakers yield high power, high interest, and high impact:

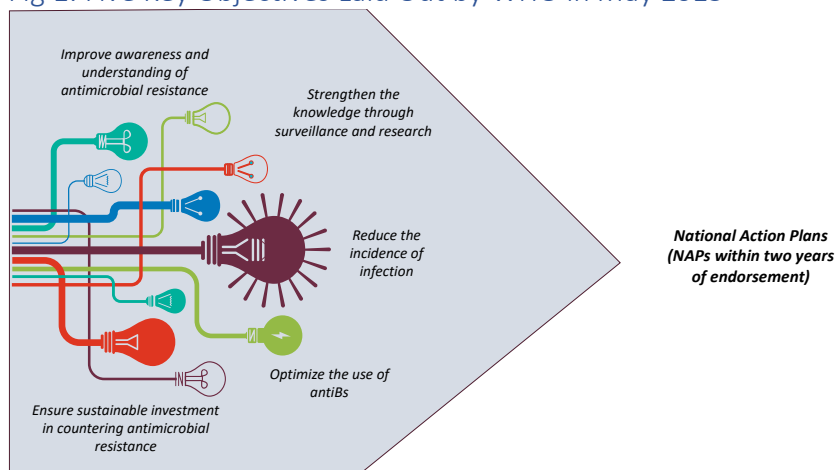
Since the WHO endorsement, there has been a lot of activity and resource allocation from different healthcare systems and respective governments to address the issue. Many participating countries have agreed and aligned to the ‘Global Action Plan (GAP)’ and draft ‘National Action Plans (NAPs)’. However, regional variance in healthcare infrastructure, socioeconomic strata, economic goals, etc. had led to poor implementation of these initiatives. Perceived healthcare orientation of AMR has led to challenges in onboarding other industries, such as agriculture, marine and environment [Appendix E], leading to a policy freeze.

Further, many policymakers have been blindsided by available data and research on AMR. In a systemic review done by (Price et al., 2018), it was found that most of the studies referring to interventions to change the public's AMR awareness and/or antimicrobial stewardship behaviour were conducted in high-income countries and recommended mass-media interventions, school-based interventions, and print-media interventions assuming universal access to these. These studies created a bias in recommendations which could have dented universal application and relevance in AMR application. For instance, the incidence of AMR across industries is substantially higher in LMICs as compared to high-income countries, where access and effectiveness of proposed interventions is limited due to multiple factors.

Section 2: Analysis of the Solution Landscape

In May 2015, the 68th World Health Assembly endorsed WHO's 'Global Action Plan (GAP)' drafted as a guiding document for participating countries to manage and reduce the burden of AMR. The GAP warranted five key objectives (Fig 1):

Fig 1: Five Key Objectives Laid Out by WHO in May 2015



Source: (WHO EMRO | Global Action Plan on Antimicrobial Resistance | Antimicrobial Resistance | Health Topics, n.d.)

However, many years after the call for NAPs, the implementation of proposed NAPs is significantly challenged. Regional bias in studies and data collected has led to defiance in

regional planning against AMR. In a systemic review of NAPs by (Willemsen et al., 2022), surveillance system was reported only by two of nine (India and Sri Lanka) SEA countries, while other countries (such as DPR of Korea, Indonesia, and Maldives) did not report any AMR surveillance.

Similarly, failure to understand reinforcing loops leading to the rising of AMR across industries [Appendix F] has led to poor outcomes. For instance, while the GAP proposes to improve awareness and understanding of AMR, none of the SEA (Southeast Asia) countries identified challenges, such as literacy rate, access to print and digital media, and limited vernacular content, etc. in their NAPs. Similarly, there is a global call out to increase funding for new antiB development, however, not many NAPs talk about engaging the VC community and incentivizing pharma to fund and develop new age antiBs [B1 Appendix F]. Moreover, the NAPs fail to acknowledge the deep structures of other industries. For instance, the GAP does not call out plans and incentives for poultry farmers to reduce antiB dependence, which can lead to a substantial drop in their yield and an increase in food prices [R7 and R8, Appendix F].

- As discussed in R5, Appendix F, the availability of cheaper Gx antiBs, potential OTC sales, and the need for cost-effective treatment leads to self-medication which in turn leads to AMR. While many of the high-income countries have a regulated distribution of antiBs, however, LMICs is the wild west. There is a need of strong regulatory and monitoring control on distribution, dispensing and use of antiBs there.
- Similarly, there is a global call to develop antiB pipeline to target drug resistance developed for existing antiB arsenal. However, as discussed in loop B1 of Appendix F, any antiB NCE post-approval will enter the same vicious cycle of use and misuse and will end up adding to the MDR problem.

The level of detail is substantially missing to help countries clearly align with global objectives and collaborate at a global level. For instance, in the GAP, ‘One Health’ is discussed once in the foreword, once in the consultative process and once in the objectives.

No clear action plan to achieve ‘One Health’ is defined.

For any global action plan to be successful, the reverse flow (local → global) is needed which can account for regional variance and identify leverage points relevant to regions and industries.

Section 3: Reframing the Problem Statement

In Appendix F, there are four major themes identified:

- **Misuse of antiBs:** The current system serves to rationalize the prescription behaviour of prescribers and reduce the use of antiBs in patients. However, it moves away from the guiding star because it does not ensure access to essential interventions, such as stewardship programs and clinical SOPs to treat infections to the prescribers (especially GPs) and does not offer intervention which can balance consumer demand for cheap food and healthcare and supply of cost-effective production.
- **Need for new antiBs or alternatives:** While the current systems call for refunding or incentivizing of antiB pipeline, however, by 2050, any new antibiotic approved will enter the same vicious cycle of the deep structure discussed in Appendix A. Further, while the proposed intervention calls out for refinancing the pipeline, however, there is limited intervention offered to solve investor’s disinterest in developing next-gen antiBs (especially compared to other TAs) and provide sustainable financing to small firms which account for 81% of the current NCEs in development.
- **Improve sanitation and living conditions to reduce water contamination and cross-infections:** the current system refers to socio-economic interventions to improve living

conditions and control water contamination; however, it is not designed to address literacy issues and enforce hygiene practices (such as social distancing). Further, as in loop R11 of Appendix F, there is a need for a system to create a closer connection between medical professionals and patients to enforce best practices to improve living standard and break chain of communicable infection in patient's own settings.

- **Enable cross-country, cross-industry collaboration – buy-in from all:** while concepts, such as ‘One Health’ call for unification of effort by different sectors and countries through advocacy and knowledge support, however, it positions the initiative to be health-oriented and does not address key concerns of the regional industries and actors. There is no clear outline or framework to address critical issues, such as the knowledge gap between the health industry and others, loss of productivity due to changes made in health / antiB policy, contain the cost of production and thereby, cost to consumer while implementing solutions related to AMR [R7 and R8 loops of Appendix F], etc.

Each industry/actor has deep structures which need interventions developed regionally. For instance, intervening other industries for rational antiB usage can lead to systemic challenges, such as food inflation. Therefore, there is a need to follow the ‘made local for global’ approach. It is important for participating countries to formulate their own action plan and global watchdog ensures implementation.

Local to the global reframed problem: *“Set up an inclusive ‘One-life’ work plan offering balancing and regional interventions to improve quality of life, manage productivity, ensure food security and address living cost inflation to motivate actors to adhere to evolving systems and reduce the use of antiBs by 30% over the next 5-years across”.*

Section 4: Interventions

1. Misuse of antiBs:

- a. Based on regional real-world evidence, set-up binding clinical protocols for the prescription of antiBs in clinical and animal care settings.
- b. Leverage serialization to track sales of antiBs and link to physician prescription—through closed-loop POB ordering system—to monitor and identify practices overusing antiBs and pharmacies offering antiBs OTC.
Draft a legal penalty for unsolicited sales and prescription of antiBs.
- c. Create green spaces and collaboration between farmers and livestock/poultry farms to ensure enough space, sharing of resources (manure and urea) and enable commercializing of bio-fuel to create alternate revenue streams.
- d. Set up digitized vet care programs and engagement to educate livestock/poultry farmers on the downside of overuse of antiBs.
- e. Set up a government-owned GPO (group purchasing organization) to control the supply of antiBs through digital distribution in animal farms.
- f. To control food inflation due to productivity loss, create a middle-man-free, government-monitored D2C supply chain using multiple channels.
 - i. Incentives, such as subsidized urea, irrigation water and electricity, can be offered to farmers and poultry/livestock farms adhering to recommended use of antiBs.

2. Need of new antiBs or alternatives

- a. To promote and sustain R&D (especially for small pharma), ‘global shared resources’ should be co-created and co-financed to fund the research and offer expertise throughout clinical development. The global platform can be self-funded by taking a revenue share of the commercialized asset.

- b. Set-up COVID vaccination similar supply and distribution chain for newly approved antiBs to reduce misuse and overprescription.
- c. Create a framework of incentives, such as grants and tax rebates, to promote R&D in antiBs. Restrict late-stage sale/entry of global pharma for NCEs nearing approval (Phase 2 and beyond).
- d. Replace tools, such as compulsory licensing and price caps, with incentives to promote local production, tech transfers and IP sharing.

3. Improve sanitation and living conditions to reduce water contamination and cross-infections.

- a. Create a PPP model to undertake WASH initiatives. Use technology to deliver vernacular content easily accessible and readable to the targeted population.
- b. Reinforce WASH initiatives through community counselling. Leverage surveillance systems to enable real-time monitoring from areas of above-average population density. Reinforce community programs, such as social distancing, especially in areas of open defecation and high population density.

4. Enable cross-country, cross-industry collaboration – buy-in from all

- a. Reposition ‘one health’ to ‘one life’ and create one advocacy group inclusive of all industries and decision-makers.
- b. Incentivize antiB behaviour by improving access and affordability to alternatives, such as urea in agriculture, phytochemicals in livestock, etc.
- c. Pesticide and chemical-free zones to promote organic farming augmented with state-sponsored D2C channel to ensure profitability for farmers. (Kumar et al., 2018)

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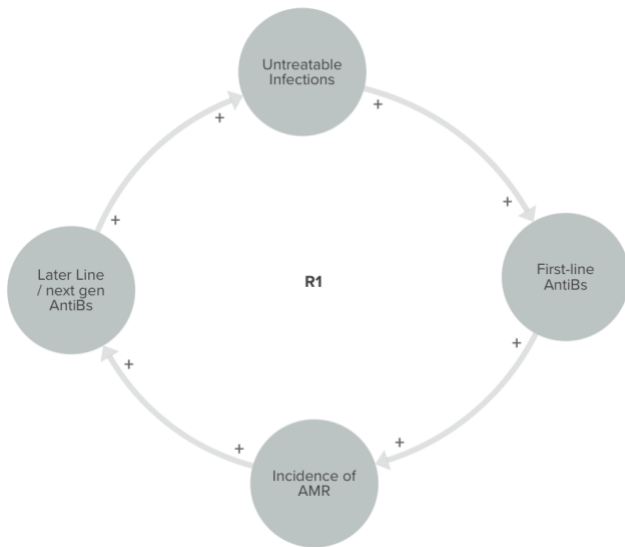
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Section 6: Appendix

Appendix A: Deep structure - AMR

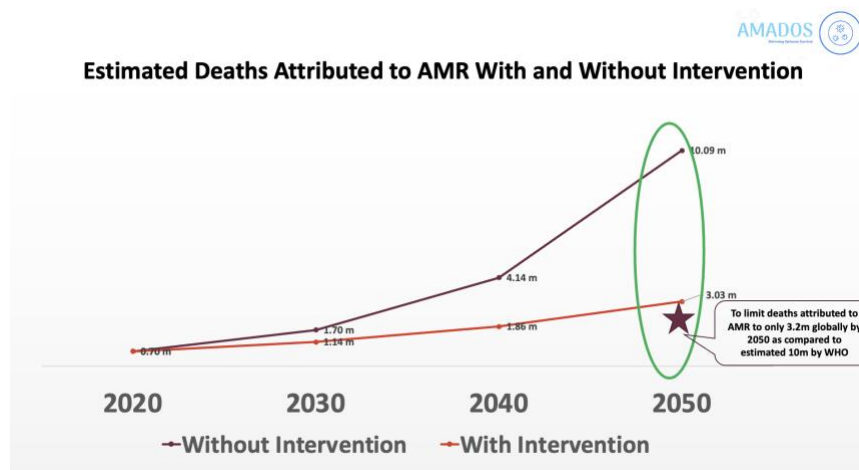


Appendix B: Antibacterial products in clinical development for priority pathogens (WHO 2022)



Source: "Antibacterial products in clinical development for priority pathogens" WHO, June 2022

Appendix C: The Guiding Star of AMADOS (Group 3) 2023 (Ref: Class Presentation)



Source: Group AMADOS (2023) Feedback - Group Presentations - The persistent problem of global antimicrobial resistance. Available at: https://canvas.sbs.ox.ac.uk/courses/2984/discussion_topics/24019 (Accessed: 18 March 2023)

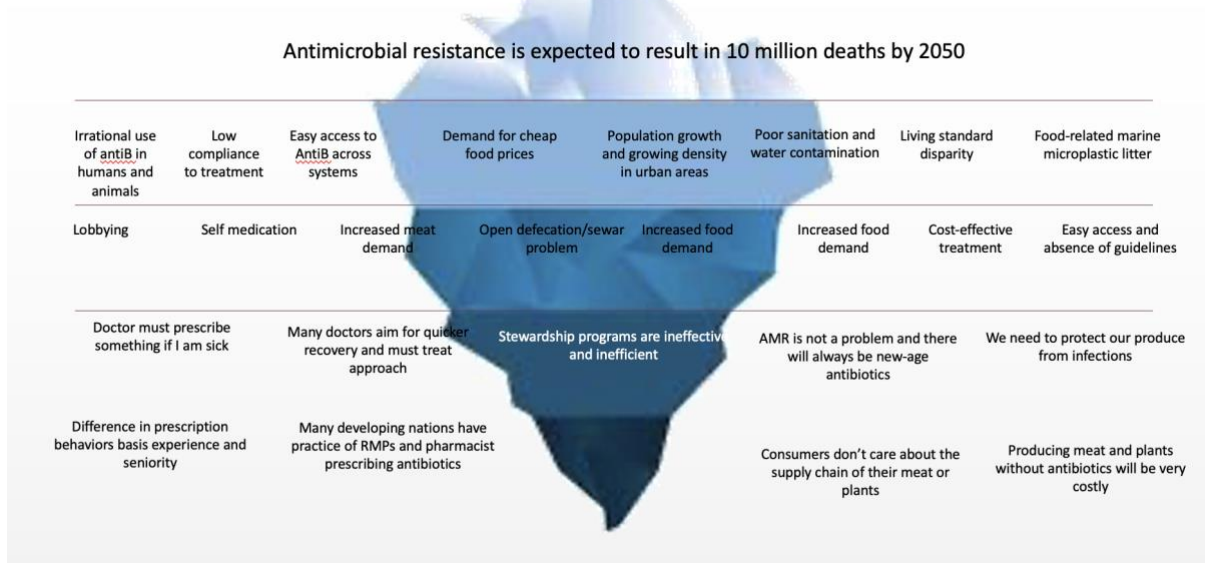
Appendix D: Stakeholder Mapping for AMR

Level	Stakeholder	Power	Interest	Impact on AMR Incidence
<i>Micro</i>	Patients	Low	High	
	Caregivers		Moderate	
	Consumers			
<i>Meso</i>	Providers			
	Pharma			
	Farmers			
	Poultry			
	Researchers			
	Inst. Administrators			
<i>Macro</i>	Regulators			
	Policymakers			
	Advisors			

Source: Group AMADOS (2023) Feedback - Group Presentations - The persistent problem of global antimicrobial resistance. Available at: https://canvas.sbs.ox.ac.uk/courses/2984/discussion_topics/24019 (Accessed: 18 March 2023); (Traversi et al., 2022), Author Analysis and Research

Appendix E: Key themes (enablers + inhibitors)

Upstream Effects			Downstream Effect		
Structural	Attitudinal	Transactional	Structural	Attitudinal	Transactional
<ul style="list-style-type: none"> Regional variance in cultural beliefs Limited governance for AMU in other industries Population growth and food safety issues Emergence of untreatable infections in poultry 	<ul style="list-style-type: none"> Social insensitivity Need outcomes quickly, 'its not my problem' Self-medication Unstructured vet care Use of pesticides / antiB in animal and plant farms improves yield and lowers cost of production. 	<ul style="list-style-type: none"> Cheaper Gx easily available as OTC in LMICs No cross-sectoral advocacy for AMU Increased pesticides and growth hormones High OOP in vet care High organic production cost / Demand of cheap food 	<ul style="list-style-type: none"> Increased mortality and morbidity Spread of AMR across multiple channels Ineffective antiBs Overstressed healthcare system 	<ul style="list-style-type: none"> Focus on near-term; no big-picture view Frequent switching on antiBs without any sensitivity analysis Inter-sectoral defiance of antimicrobial abuse 	<ul style="list-style-type: none"> Rise in multi-drug resistance in animals; food chain pollution Unwillingness to invest and regulate use of antiBs across industries Enlisting of new-age antiBs as essential medication to reduce cost and improve access Regulating antiB use across industries can lead to food inflation and other cost rise
<ul style="list-style-type: none"> Access and affordability variance; limited AMR awareness in patients High OOP; long GP ques No stewardship programs targeting primary and secondary care 	<ul style="list-style-type: none"> Need cheap medication. Quick recovery Self-medication and low adherence AMR is an ICU problem Quackery and prescriptions by pharmacist Use of antiB in viral infections 	<ul style="list-style-type: none"> Cost-effective Gx antiB available OTC in few regions Low compliance to guidelines at primary and secondary level Lobbying with doctors 	<ul style="list-style-type: none"> Emergence of MDR infections and pathogens Increase in comorbidities and cross infections. Long-term use of antiBs Unstructured antiB rotation Increased use of broad-spectrum new gen antiBs, such as carbapenems 	<ul style="list-style-type: none"> Quick recovery from infection is critical compared to AMR AMR is long-term impact and one-time use will not hurt Use carbapenems early to reduce use of multiple antiBs 	<ul style="list-style-type: none"> Increasing overall cost of therapy Up to 10X cost to treat MDR infections; increased burden on health systems. Economic losses due mortality and loss of DALYs
<ul style="list-style-type: none"> Poor literacy rate and living conditions in some regions Limited healthcare access and awareness Low affordability Poor hygienic conditions and close spaces for both, humans, and animals Open defecation Poor sewerage 	<ul style="list-style-type: none"> Waste dumping and poor waste management Water pollution Poor defined and complied safety norms in hospitals and manufacturing industries Limited compliance to social distancing 	<ul style="list-style-type: none"> Rising antibiotic pollution and natural resources (water and soil) pollution Exposure of pathogens to multi-drugs and chemicals Lobbying to prevent any regulatory control to reduce use of antiBs and pesticides 	<ul style="list-style-type: none"> Increased incidence of cross infections, droplet infections and MDR infections Growing population of MDR pathogens in marine ecosystem Increased mortality and morbidity in patients, plants and animals Inefficient surveillance systems Cross border transfer of MDR pathogens 	<ul style="list-style-type: none"> WASH and hygiene maintenance is government's responsibility Growing evidence of impact of poor hygiene and living conditions, and AMR and related mortality and morbidity Rise of cross infection, such as MDR TB in lower income strata leading to increased mortality 	<ul style="list-style-type: none"> Underfunded WASH initiatives have led to poorly implemented initiatives. Growing evidence of impact of poor hygiene and living conditions, and AMR and related mortality and morbidity Rise of cross infection, such as MDR TB in lower income strata leading to increased mortality
<ul style="list-style-type: none"> Rapidly growing demand for antiBs due to population growth Many pathogens have developed resistance towards available antiBs Emergence of superbug High cost of development and low success rate Generic invasion and price caps for antiBs 	<ul style="list-style-type: none"> High revenue and high growth TAs, such as cancer, are more critical for company portfolio Development of MDR has increased risk of development for antiBs Unstructured and inconsistent incentive by healthcare systems to explore new antiBs AMU leading to AMR is a vicious cycle and will happen 	<ul style="list-style-type: none"> Most of the ongoing clinical development is focused on priority pathogens Global MNCs have limited pipeline. Regional / small companies are driving research Gx, legal interventions (compulsory licensing) and price caps have limited the revenue potential of new drug development 	<ul style="list-style-type: none"> Only one novel antiB was approved over the last 35 years Increased mortality and morbidity linked to AMR and MDR pathogens LOE achieved for most of the available antiBs, leading to easy access and misuse across industries 	<ul style="list-style-type: none"> Smaller companies need incubator and financial support from the health systems to fund their research Lack of research and novel therapy has turned AMR into global pandemic 	<ul style="list-style-type: none"> Small companies discovered 81% of the antiBs in clinical development. (Thomas & Wessel, 2022) During 2019-2020, while the venture funding for oncology drugs increased by 40%+ annually to reach \$6.9 bn, however, for antiBs, it was stagnant on \$0.2 bn.
<ul style="list-style-type: none"> Regional variance No law binding action Most of the AMR studies are done in developed systems, however, incidence is higher in LMICs (Price et al., 2018) Inconclusive surveillance data leading to ineffective engagement & policy making 	<ul style="list-style-type: none"> Profits and outcomes are preferred over AMR Me-first approach Conflicts between departments and actors and systems Priority given to controlling food prices, improving patient outcomes, and focus 	<ul style="list-style-type: none"> Multiple departments, industries, and actors with limited alignment on objectives and goals AMR is a third-world problem 	<ul style="list-style-type: none"> Most of the initiatives and policies are either focused on healthcare or are relevant at regional level Despite call for One Health, the process and engagement of stakeholders and industries is disconnected. 	<ul style="list-style-type: none"> Absence of clear guidelines and regulations have created actors from different industries question their relevance. Confused and convoluted plans with no clear action points 	<ul style="list-style-type: none"> Disproportionate allocation of resources. High-income countries claim significant progress, while LMICs call for more human and financial resources. Economic impact of AMR on various industries is challenged in absence of conclusive data. Poor alignment, inadequate resources, and weak implementation



Source: (Traversi et al., 2022), Group AMADOS (2023) Feedback - Group Presentations - The persistent problem of global antimicrobial resistance. Available at:

https://canvas.sbs.ox.ac.uk/courses/2984/discussion_topics/24019 (Accessed: 18 March 2023)