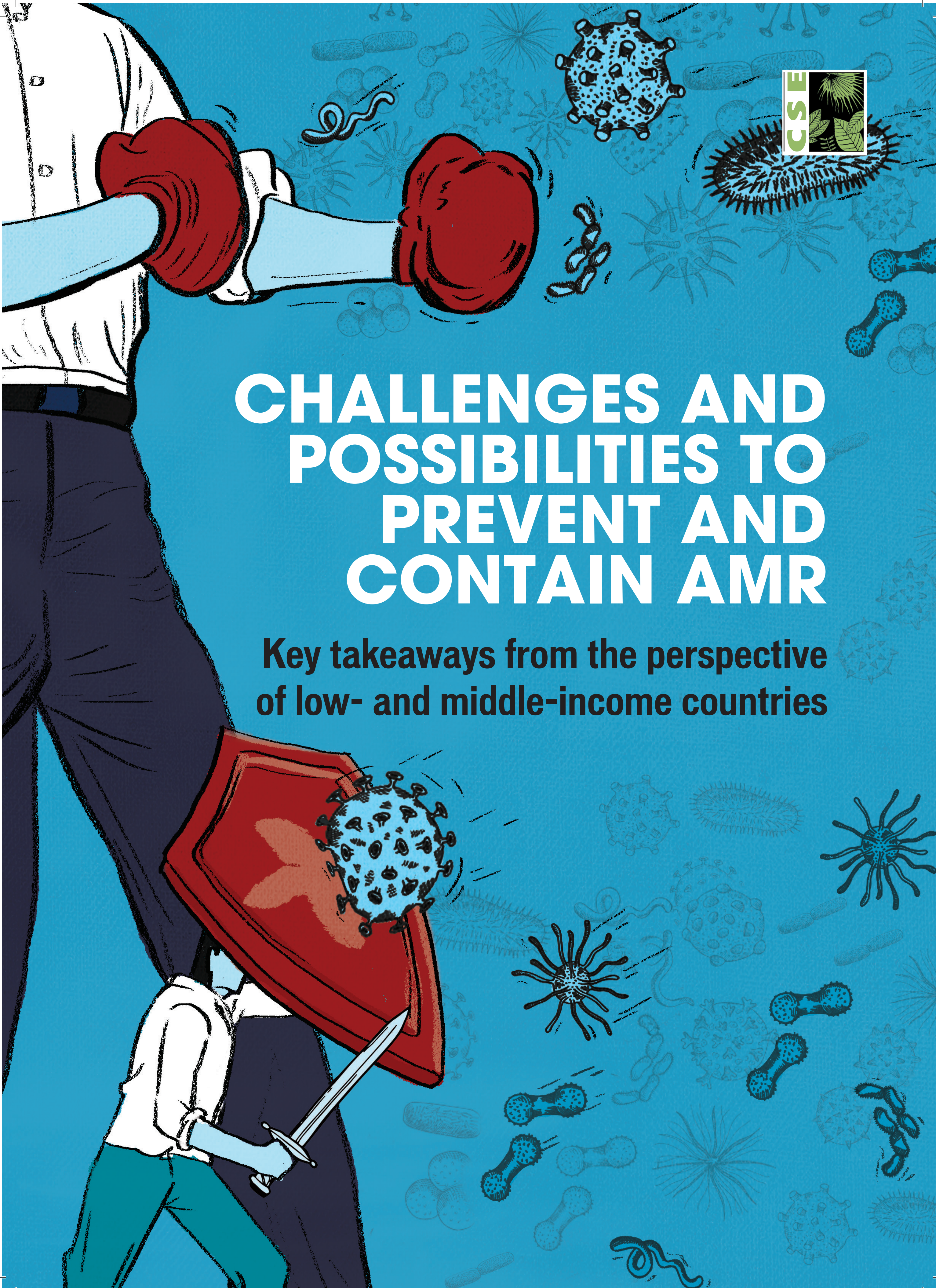

CHALLENGES AND POSSIBILITIES TO PREVENT AND CONTAIN AMR

Key takeaways from the perspective of low- and middle-income countries

CHALLENGES AND POSSIBILITIES TO PREVENT AND CONTAIN AMR

Key takeaways from the perspective of low- and middle-income countries

CENTRE FOR SCIENCE AND ENVIRONMENT

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1
INTRODUCTION

INTRODUCTION

That bacteria can kill us is once again becoming a concern after over half a century. The world is more conscious than ever that the power of antibiotics to treat infections is silently getting eroded. Known as antimicrobial resistance (AMR), or antibiotic resistance in particular, this crisis has begun to get the attention it deserves. The momentum to save the effectiveness of existing antibiotics is growing.

In September 2024, member states of the United Nations will discuss and commit to future action on AMR at a high-level meeting during the General Assembly in New York. The last time they met in 2016, they came up with a political declaration.

Experts worldwide see this as a big opportunity for stronger global action against the global threat of AMR. Bold outcomes, specific commitments and targets are expected. This is a big ask. The key challenge is to have countries with hugely varying situations agree on specifics.

The drivers and levels of AMR vary among countries, and the resources to fight against it differ even more. But, importantly, what is agreed on can potentially impact development, trade and livelihood of nations in different ways.

Like every negotiation, the challenge of consensus gets partly addressed if the entire group is adequately aware of where everyone currently stands and what they can do in the future. A good understanding about what can work in low- and middle-income countries (LMICs) will make a huge difference.

For example, access to antibiotics for treating preventable infections remains a big worry in LMICs. They also need to produce more food for nutrition for a big part of the global population. Their food systems are likely less dependent on chemicals, and geared towards providing livelihoods to millions of small farmers. Solutions available to them will scale up only if they are cost-effective. Prioritizing 'prevention' is their best bet and they can't be expected to invest in resource-intensive processes.

Solutions in these settings are also emerging. The success of ethnoveterinary medicines in the Indian diary sector has helped reduce antibiotic use while maintaining productivity and livelihoods. All such local solutions in different countries need to be recognized and encouraged. Moreover, countries would like to set targets based on their own situations.

This report tries to inform about such challenges and possibilities. A broad outline is presented for select areas related to, for example, access to effective antibiotics, sustainable food systems, managing environmental AMR spread, and implementation of national AMR action plans.

The key takeaways are based on CSE’s work in India and engagements with African and Asian countries as well as global stakeholders. The report provides a snapshot of CSE’s work on AMR, which started over a decade and a half ago. At the core of this work is the evidence and learnings developed from the ground and a perspective that is aligned to sustainable and equitable development of the Global South. The report includes CSE’s first study on this subject conducted in its laboratory in 2010 on antibiotic residues in honey. It also mentions a recent assessment, done in 2023, on antibiotic pollution from manufacturing.

The report also captures CSE’s work in Zambia to help implement the national AMR action plan and learnings from multiple engagements with African, Asian and global colleagues.

We hope that the challenges and possibilities outlined help the deliberations aimed at influencing outcomes of the high-level meeting at the UN General Assembly. The world needs a well-coordinated action against AMR that considers ground realities of all countries.

We also hope that the report helps our colleagues in LMICs to prioritize their efforts against AMR.

2
ACCESS TO EFFECTIVE ANTIBIOTICS

ACCESS TO EFFECTIVE ANTIBIOTICS

2.1 CHALLENGES

- **The crisis of AMR is not limited to the crisis of antibiotic R&D. It is in fact a triple crisis**. On the one hand, antimicrobial resistance is rising and antibiotics are becoming ineffective. On the other, new antibiotics that can meet the current public health need are not being adequately developed. But, most importantly, it is the crisis of 'access' to existing as well as newly developed effective antibiotics by everyone in need at affordable prices. All three crises are linked.

- **'Access' concerns are relevant in many countries but are more prominent in low- and middle-income countries (LMICs)**, where it is also a bigger concern than 'excess' and still very much applicable for older antibiotics in addition to newly developed antibiotics. Reasons include costs and challenges in approvals, registration, licensing and marketing in view of expected returns due to low sales volume and revenues; weak healthcare systems and reimbursements mechanisms leading to greater out-of-pocket expenses making required antibiotics unaffordable; limited support from diagnostics that impacts stewardship practices and treatment effectiveness; inadequate mechanisms and controls on drug quality, procurement and availability; and weak supply chains often marred by disruptions.

- **With several infections becoming difficult to treat, future 'access' to effective treatments is dependent on development of new antibiotics.** But the current antibiotic pipeline is not promising. It is not future-ready. This is because major pharmaceutical companies have left the space of antibiotic development. Most exited decades ago and others in recent years. But this 'big exodus' is not only because of the high risk and low return of antibiotics. It is also because of humongous profits that drugs for cancer and non-communicable diseases (NCDs) such as autoimmune, metabolic and neuro-degenerative diseases can make. Only few big companies are developing antibiotics and the responsibility is now shifted to small- and medium-scale antibiotic developers, which are struggling to overcome big hurdles.

- **The global response to antibiotic innovation crisis has seen limited success so far.** Despite the high public-health risk of AMR, society and healthcare systems place a low value on antibiotics. The response is now gaining momentum, but there are big gaps. The big companies that once made huge profits from antibiotics are far from entering back into antibiotic development. They are expecting big support from governments. Their own initiatives to help the cause are much less than required. Efforts to develop and make available new antibiotics not adequately focusing on clinical needs of the LMICs is also a valid concern.

2.2 POSSIBILITIES

It is clear that there is a need for reforms and measures at the global level to stimulate the antibiotic R&D ecosystem for a sustainable and equitable access to effective antibiotics across the world, including in low- and middle-income countries. At a broad level, this means:

- **Governments should come together and play a greater role** towards a coordinated response as individual country efforts will have limited long-term gains. Collective action is expected to be led by major economies such as the G20 nations.

- **Greater public financing and reforms on several aspects** such as related to market, reimbursements, regulatory approvals, cost of new antibiotics and clinical trials.

- **Balance in public–private partnership** as governments need not solely take up entire antibiotic innovation and public financing should not just be about bringing back major pharmaceutical companies into antibiotic R&D.

- **The major pharmaceutical companies of the world should do more**. They have made huge profits from antibiotics. They know the science and business of it very well and should play a much bigger role than they are currently playing.

- **Access to antibiotics must be integrated with all measures supporting antibiotic innovation**.

- **Antibiotics do not fit into the conventional definition of 'global public good'**. There could be different dimensions or characteristics such as antibiotic effectiveness or AMR containment that can be considered, if needed. Antibiotics are talked about to be considered as a 'global public good' to increase public financing, but the conventional definition of global public goods is narrow and there is a need felt for a broader concept of public goods.

SPECIFICALLY,

- **In addition to funding, global coordination should aim to avoid a fragmented response** among stakeholders like governments, large-, small- and medium-scale antibiotic developers, academia, funders and civil society. This may include assessing gaps in the pipeline, prioritizing antibiotics and developers; predicting demand and setting targets for a robust pipeline that is well informed by global public health needs; designing, testing and piloting agreed-upon incentives; harmonizing regulations and removing access barriers.

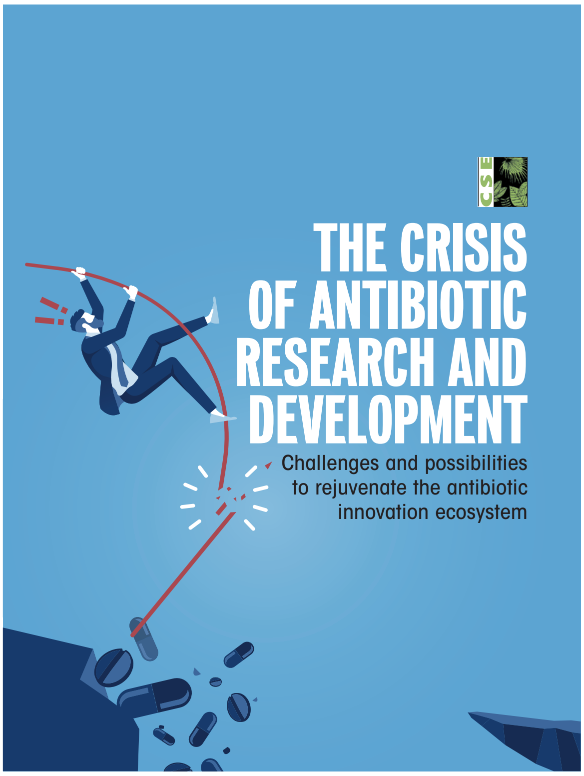
- **With insufficient investments, there is need for increased financing that is predictable, resilient and sustainable.** 'Push' incentives are working but they cannot serve the entire purpose alone. They can be tied up with 'pull' incentives, which are more recent and there is a need to build on the experience of countries currently implementing 'pull' incentives. But, importantly, there is a need to think beyond these two sets of funding mechanisms.

- **Non-financing measures like regulatory harmonization should also be focused upon** such as in scientific and technical requirements, analytical procedure development and validation, quality risk management, study design/sampling, cohort recruitment for quality, safety, and efficacy assessment. Harmonization will benefit in favourable marketing conditions to support early access to medicinal products, promoting competition and efficiency, and reducing unnecessary duplication of clinical testing.

- **Small- and medium-scale antibiotic developers in particular need to be supported** through, for example,:
    - Adoption of clearly defined pathways for accelerated approval of antibiotics at the national level along with streamlining of approval processes to minimize bottlenecks;
    - Encouraging balance between a viable and well-differentiated product for unmet need in the short-term and an innovative drug carrying more failure risk for the longer term;
    - Support for clinical trials of innovative drugs such as through expanding clinical trial networks and capacity and helping conduct trials in other countries;
    - Collaboration platforms with academic institutes and big pharmaceutical companies with, for example, the help of funding agencies;
    - Nurturing and conserving the discovery of talent for sustainable long-term innovation; and
    - Local, national and/or regional funding support in LMICs as big funding otherwise depends on the scale of the problem of resistance in high-income countries.

2.3 SNAPSHOT OF CSE'S WORK ON THE CRISIS IN ANTIBIOTIC R&D

A. THE CRISIS OF ANTIBIOTIC RESEARCH AND



Cover story and report on the crisis of antibiotic research and development, 2023

DEVELOPMENT

Rationale: To understand the state of antibiotic pipeline, reasons for its lack of promise and what can be done

Key findings:[1,2]

- **The antibiotic pipeline is weak and lacks promise for the short term and long term**

There were just 45 traditional and 32 non-traditional antibacterial candidates in active clinical development as per WHO data on

Table 1: Antibacterial clinical pipeline

	Phase 1	Phase 2	Phase 3	Pre-registration	Total
Traditional candidates	22	14	9	1	46
Priority pathogens	16	3	8	1	28
Mycobacterium tuberculosis	6	7	-	-	13
Clostridioides difficile	-	4	1	-	5
Non-traditional candidates	12	15	5	2	34
Priority pathogens	7	10	3	1	21
Mycobacterium tuberculosis	1	-	-	-	1
Clostridioides difficile	4	5	2	1	12
Total	34	29	14	3	80

Source: CSE analysis of WHO data on antibacterial candidates in clinical pipeline updated till late 2021; - denotes no candidates

antibacterial products in the clinical and pre-clinical pipeline updated until late 2021.

Out of the 45, only 28 target WHO priority-pathogens. There were only nine products in Phase 3 of clinical development, of which only two target WHO critical-priority pathogens. There are no products for *Mycobacterium tuberculosis*. Among the 32 non-traditional candidates, only five are in Phase 3. For *M. tuberculosis*, there is only one candidate which is in Phase 1 (see *Table 1: Antibacterial clinical pipeline*).

In comparison, there are more than 10,000 medicines in active clinical development for cancer, more than 1,800 for neuropsychiatric conditions and about 1,500 for endocrine, blood and immune disorders.

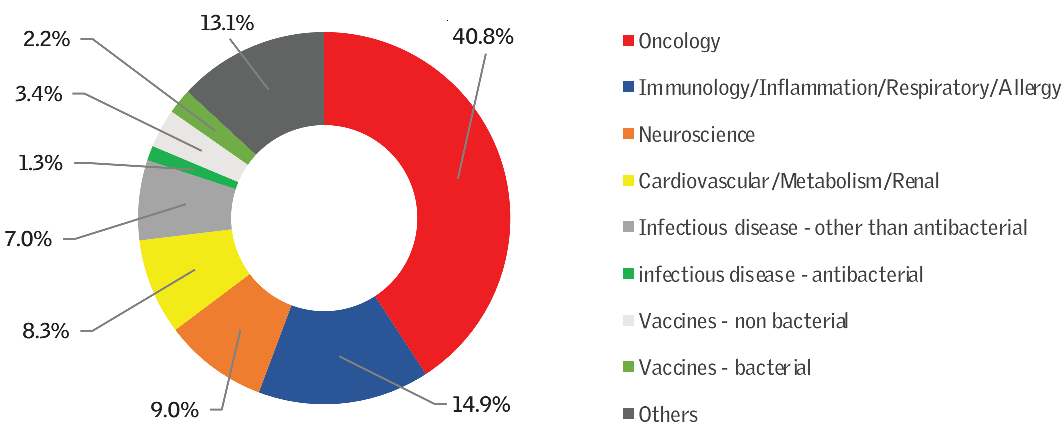
In the case of the 217 candidates in pre-clinical pipeline, only 34 (~15 per cent) are in late-stage development. Investigational new-drug applications have been submitted for only three of these.

- **Big exodus of pharmaceutical companies from antibiotic R&D**

The clinical development pipeline of 15 high-earning global pharmaceutical companies were analysed on the basis of their websites. The companies were Astra Zeneca, F Hoffman-La Roche, Bristol Myers Squibb, Pfizer, Novartis, GlaxoSmithKline, Johnson & Johnson, AbbVie, Gilead Sciences, Sanofi, Eli Lilly and Company, Merck & Co, Amgen, Biogen and Viatris. Collectively, their 2022 revenue was about US $711 billion and a considerable 17.5 per cent (US $124 billion) was invested in research and development. As in June 2023, out of the 1,007 molecules in the clinical pipeline of these companies, only 13 (1.3 per cent) antibacterial candidates were found to be developed by four companies. GSK was developing eight of them. F Hoffmann-La Roche and Pfizer were developing two each and AbbVie was developing one.

In contrast, 411 candidates (41 per cent) were being developed for cancers/oncology by 13 companies. Almost all companies were involved in developing 150 candidates (15 per cent) in areas of immunology, inflammation, respiratory or allergy. A total of 91 candidates (about 9 per cent) were being developed in areas of neurosciences. A total of 84 candidates (8.3 per cent) were being developed in areas of cardiology, metabolism or renal (see *Graph 1: Pipeline summary of 15 select pharmaceutical companies*).

Graph 1: Pipeline summary of 15 select pharmaceutical companies



Source: CSE analysis based on pipeline information of company websites. Note: Others include rare blood disorders, rare disease, hematology, ophthalmology, pain, pulmonary hypertension and aesthetics.

A detailed analysis of the clinical pipeline of the individual companies shows that almost all focus on areas other than antibacterial candidates. Key focus remains oncology for most companies (see *Table 2: Pipeline of 15 select pharmaceutical companies*).

The shift of the focus is also marked by their entry into mergers and acquisitions to strengthen their pipelines in other disease areas. Many of these have been pioneers or very active in antibiotic R&D at one point of time.

'Market failure' for antibiotics is often cited as a reason as revenues from selling an antibiotic are often low and unpredictable due to reasons like short duration of most antibacterial treatments compared to treatment for chronic conditions and uncertain nature of the need. Due to stewardship concerns, antibiotic developers also cannot push to sell their drugs at least in the first few years and by the time a new antibiotic becomes the first or second line of treatment in a country, there is a risk of losing revenues to the low-cost generic options. But this big exodus is also due to high revenues and profitability in other disease areas. For example, a review of the top 10 blockbuster drugs sold in 2021 shows how drugs for cancer, autoimmune diseases and diabetes-related complications can be profitable.

Table 2: Pipeline of 15 select pharmaceutical companies

Company and annual revenue (2022)	R&D expenditure in 2022 (per cent of overall revenue)	Total number of molecules	Clinical pipeline focus
AstraZeneca plc USD 44.4 bn	USD 9.7 bn (21.8%)	170	Oncology [95], cardiovascular, renal and metabolism [24], respiratory and immunology [28], rare disease [15], vaccine and immune therapies [3], others [5]
F. Hoffmann-La Roche AG CHF 63.2 bn	CHF 14 bn (22.1%)	104	Immunology [11], infectious diseases [5]; **bacterial [2]**, metabolic[1], neuroscience[24], oncology/hematology [51], ophthalmology[11], others [1]
Bristol-Myers Squibb USD 46.1 bn	USD 9.5 bn (20.6%)	91	Solid tumors [47], hematology [22], immunology [10], fibrotic disease [2], cardiovascular [6], neuroscience [4]
Pfizer Inc. USD 100.3 bn	USD 11.4 bn (11.4%)	89	Anti-infectives [7]; **bacterial [2]**, rare diseases [12], inflammation and immunology [14], internal medicine [10], oncology [32], vaccines [14; **bacterial [6]**]
Novartis AG USD 50.5 bn	USD 9.9 bn (19.6%)	81	Biosimilars [2], cardiovascular [8], global health [9]*, hematology [14], immunology[15], neuroscience [9], ophthalmology [4], respiratory and allergy [2], solid tumors [18]
GlaxoSmithKline plc GBP 29.3 bn	GBP 5.4 bn (18.4%)	75	Infectious diseases [41; **bacterial [8]**, **bacterial vaccine [10]**], HIV [6], oncology [16], immunology-respiratory [8], opportunity-driven [4]
Johnson & Johnson USD 94.9 bn	USD 14.6 bn (15.4%)	74	Cardiovascular and metabolism [7], immunology [12], infectious diseases and vaccines, global public gealth [14], **bacterial vaccine [1]**, neuroscience [8], oncology [28], pulmonary hypertension [5]
AbbVie Inc. USD 58 bn	USD 7.1 bn (12.2%)	63	Immunology [7], neuroscience [10], oncology [26], eye care [3], aesthetics [10], other specialities [7]; **bacterial [1]***
Gilead Sciences, Inc. USD 27.3 bn	USD 5 bn (18.3%)	60	Viral diseases [17], inflammatory disease [4], oncology [38], fibrotic diseases [1]
Sanofi S.A. EUR 42.9 bn	EUR 6.7 bn (15.6%)	53	Oncology [15], immunology and inflammation [14], neurology [5], rare blood disorder [4], rare disease [5], vaccines [10; **bacterial 3**]
Eli Lilly and company USD 28.5 bn	USD 7.2 bn (25.3%)	50	Cancer [9], diabetes and obesity [20], immunology [10], neurodegeneration [7], pain [4]
Merck & Co., Inc USD 59.2 bn	USD 13.5 bn (22.8%)	39	Antiviral [5], cardiovascular [4], endocrinology [1], neuroscience [2], oncology [22], respiratory [2], vaccines [3; **bacterial [2]**]
Amgen Inc. USD 26.3 bn	USD 4.4 bn (16.7%)	36	Bone [2], cardiometabolic [4], hematology/oncology [18], inflammation [9], metabolic disorders [1], nephrology [1], neuroscience [1]
Biogen Inc. USD 10.1 bn	USD 2.2 bn (21.8%)	22	Alzheimer's disease and dementia [5], genetic neurodevelopmental disorders [1], multiple sclerosis [2], neuromuscular disorders [3], neuropsychiatry [2], neurovascular [1], Parkinson's disease and movement disorders [5], specialized immunology [3]
Viatris Inc. USD 16.2 bn	USD 0.66 bn (4.1%)	NA	Cardiovascular, neurology, pain/osteoarthritis, urology, psychiatry

*Includes infectious disease; NA: Data not available; Note: Data is updated as per June 2, 2023

- **Small- and medium-scale antibiotic developers are facing challenges**

With the exit of big pharmaceutical companies, micro-, small- and medium-scale companies are becoming active in antibiotic R&D. About 84 per cent (183) of total 217 preclinical candidates are being developed by micro (≤ 10 employees), small (11–50 employees) and medium (51–500 employees) developers, of which 70 per cent are by micro and small developers.

Many of these companies have had their share of challenges. In the recent past, some of them filed for bankruptcy or faced diminished values and exits. From the LMIC point of view, there are challenges linked with lack of regulatory harmonization and problems related to clinical trials and funding for resistance, which are not greatly prevalent in rich countries. Some LMICs had to start developing other drugs in, for example, the area of oncology along with antibiotics. Others had to focus on products such as probiotics for use in the animal sector.

The study also outlines key push and pull strategies to support antibiotic innovation and whether considering antibiotics as 'global public goods' can help the cause. A Down to Earth *cover story 'Whither new antibiotics' was published first. The findings were then discussed over a series of public webinars with national and global experts. Subsequently, a discussion paper 'The Crisis of Antibiotic Research and Development' was published.*

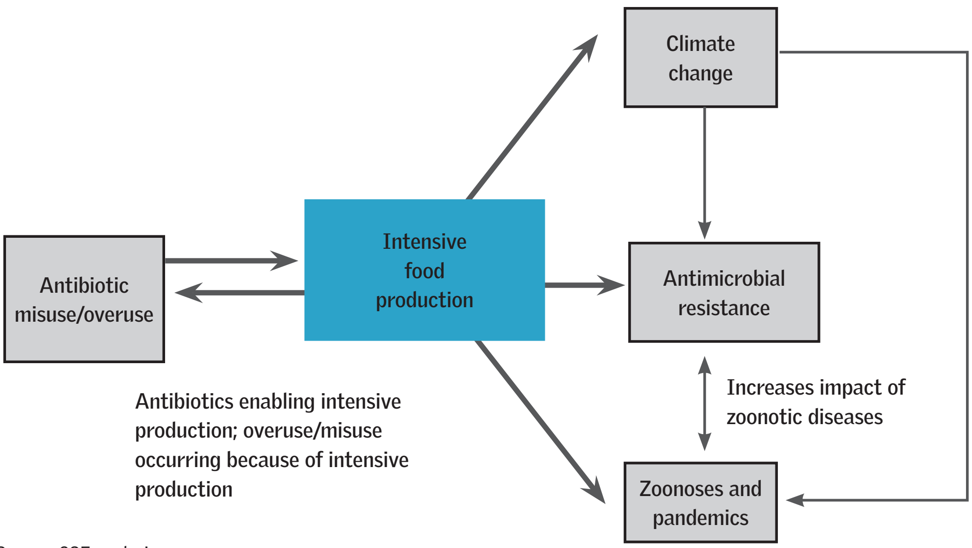
3
SUSTAINABLE FOOD-PRODUCTION SYSTEMS

3.1 CHALLENGES

- **Food from animals is produced in intensive systems driven more than ever by demands and commercial interests**. Characterized by large-scale factory-like settings, these systems have high stocking density of genetically selected similar but not disease-resilient breeds kept under confined conditions with limited focus on animal husbandry and greater dependence on commercial feed, chemical inputs and automated systems. These chemical-intensive systems are not just a potential breeding ground for zoonotic diseases, resistant pathogens and pandemics but also impact biodiversity and are intensive sources of greenhouse gas (GHG) emissions (see *Figure 1: Linkage between antibiotic use and AMR, climate change, zoonoses and pandemics*). These unsustainable disease-prone settings are hugely dependent on antibiotics as an easy and economical solution. At a broad level, it could be said that food-animal production in LMICs is less intensive compared to high-income countries.

- **Growth promoter use of antibiotics still in practice.** Eliminating the misuse of antibiotics as growth promoters such as in the poultry sector has by and large received

Figure 1: Linkage between antibiotic use and AMR, climate change, zoonoses and pandemics



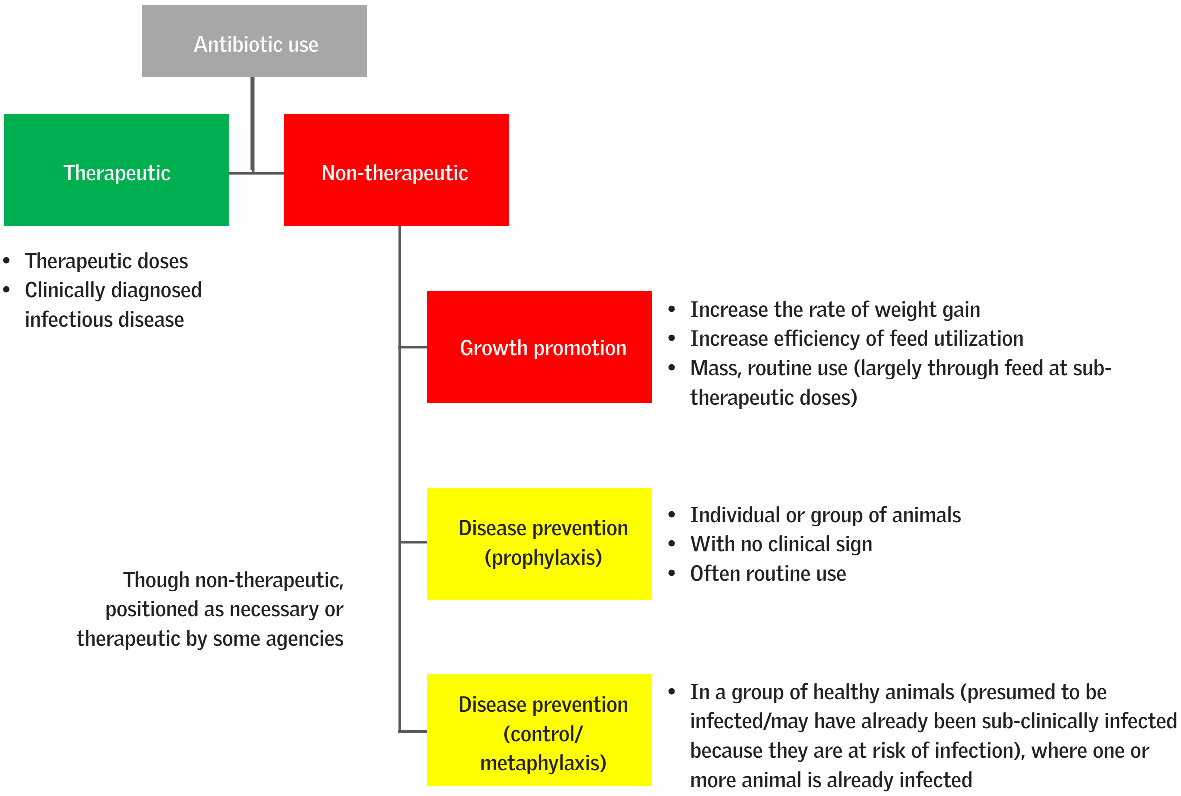
Source: CSE analysis

consensus among global governance, but there still are many countries that do not regulate such use or even more wherein such misuse through feed is part of the practice. Such use could still be a possibility in high-income countries other than of the European Union (EU), which banned antibiotic growth promoters over two decades ago. Some LMICs have also initiated controls on some or all antibiotics, but by and large stakeholders in LMICs often cite, perhaps realistically so, the lack of alternatives, resources and economical options as well as highlight concerns related to disease-prone conditions, food security, livelihood, development and trade needs.

- **Antibiotic use for so-called 'disease prevention' is far from 'real prevention'**. While the EU banned group-preventative use of antibiotics in food animals from 2022, the guidance from global governance structures—which in particular is closely looked up to by stakeholders in LMICs—at a broad level, does not recognize this non-therapeutic use as a 'misuse', which continues to remain a common practice across food-animal sectors in most countries. Antibiotic manufacturers and stakeholders with commercial interest endorse this use as it can offset the losses due to stricter controls on growth-promoter use. Stakeholders in LMICs often cite similar concerns as in the case of eliminating growth-promoter use (see *Figure 2: Types of antibiotic use/misuse in food-animals*).

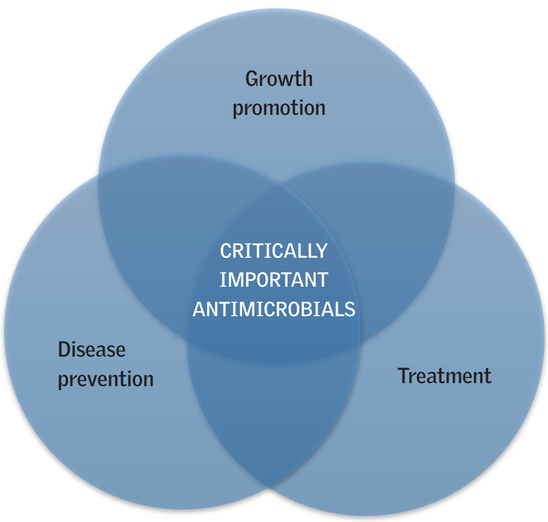
- **Significant overlap in antibiotics used in food production and to save human lives.** Many antibiotics are considered critical for humans and are used against difficult-to-treat resistant infections or as a last-resort to save lives (see *Figure 3: Use of critically important antibiotics in food-animals*). The global guidance from responsible agencies lacks consistency and has not been able provide a simple and practical solution that country-level human- and animal-sector stakeholders can easily adopt. There have been restrictions in some countries on a few or more types of critical antibiotics. But, largely, stakeholders in LMICs appear less prepared to handle this issue.

Figure 2: Types of antibiotic use/misuse in food-animals



Source: CSE analysis depicting definitions and practice.

Figure 3: Use of critically important antibiotics in food-animals



Source: CSE analysis depicting practice

- **Global understanding on the quantity of antibiotics used in food-animals remains weak.** Other than for the countries of the EU, for many countries it is not known how much of different antibiotics are used across food-animal sectors at the national level. This baseline understanding on antibiotic use is missing, which would also help them to meet commitments made as part of Muscat Manifesto, 2023. There is not much national-level understanding on antibiotic resistance in food-animal sector either.

- **Food-animal production systems in LMICs are different.** It is largely about livelihoods of small farmers and not just about profits for a few. It is also about development and trade of the country and nutrition of a large part of their population. Though the situation could be changing, small farmers in these settings were historically not dependent on antibiotics. They are also less prepared to suffer productivity loses and adopt expensive solutions related to, for example, biosecurity, alternatives and vaccines.

- **Cost-effective AMR-safe waste management needs attention.** The need of the hour is to manage waste from food-animal farms to make it AMR safe for use in agriculture and/or animal production settings and leveraging resource efficiency by following principles of circularity.

- **The role of meat consumption is not discussed in addressing the challenges of AMR,** in addition to the challenges of environment, biodiversity and climate change.

3.2 POSSIBILITIES

There is no dearth of the much-needed specific measures as highlighted by several global guidances and national action plans along with how to implement them and the challenges that LMICs need to overcome. At a broad level, the following can be noteworthy for LMICs.

- **'Prevention' should be central to all strategies and approaches aimed at food-animal systems**. LMICs will find it difficult to afford the cost of AMR and containing it. Solutions that help prevent the crises are likely to be readily adopted by policymakers and individual farmers. With limited resources and capacity, the best bet for stakeholders in LMICs would be to invest and incentivize preventive approaches. This could mean focusing on growing food in a way that helps prevent the occurrence of disease at its first place or help avoid the use of antibiotics. This could mean focusing on animal health as well as investing more in alternatives, biosecurity and vaccination.

- **Solutions must be cost-effective for farmers of this part of the world.** Often such low-cost solutions arise from local and indigenous settings, which needs to be encouraged instead of expensive top-down or industry-pushed approaches that are more suitable for high-income countries. Cooperative movements or small-scale decentralized production and procurement can pave the way. Ethnoveterinary-medicine-based approaches can be tested and scaled up.

- **Conserving critical antibiotics should be the aim**. If antibiotic use is unavoidable, those which are critical for humans should be avoided without compromising animal productivity and welfare. All national-level efforts should be aligned and so should be global interventions. This also means, that all misuse in growth promoters and so-called disease prevention needs be eliminated, which can only happen if alternative solutions are found, incentivized and promoted.

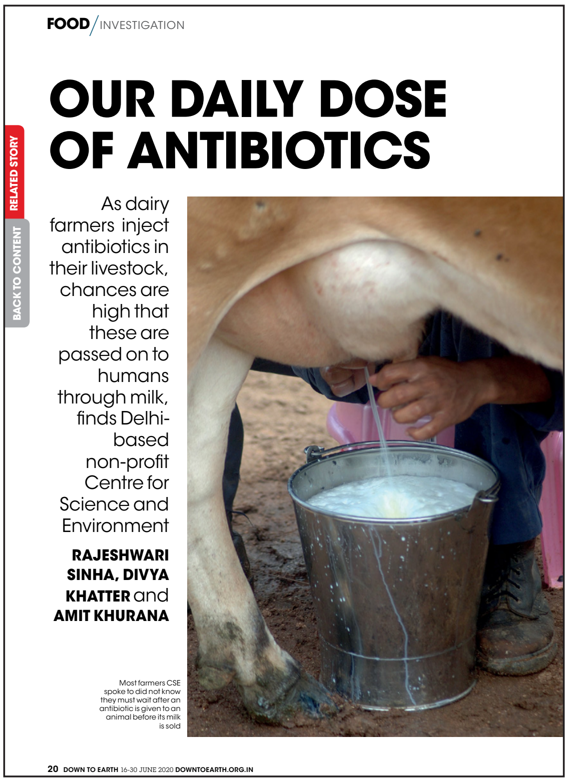
- **Development, livelihood and nutrition security needs of LMICs should be recognized and supported.** Most LMICs will have to grow their own food for nutrition needs of their population, livelihood needs of their farmers and development plans of the country. Global plans and commitments should therefore provide the required flexibility and avoid pushing interventions that can jeopardize these domestic goals. LMICs need to be supported to produce more food but sustainably and targeting LMICs unreasonably must be avoided.

- **LMICs have an opportunity to leapfrog towards more sustainable ways of producing food**. Food systems in many of these countries would not be as intensive as in many high-income countries. Such LMICs have greater chance of not only reducing antibiotic use further but also successfully transition and transform their food systems that are friendly for public health, livelihood, environment and biodiversity. These co-benefits also make a strong case for investing in transition for the long-term.

- **Countries should have the flexibility to set their own targets** such as for reduction in antibiotic use or antibiotic resistance, overall or specific to a class or in a sub-sector. Targets therefore should be differential and abundantly informed by the local context and ground realties, which can vary based on several factors.

3.3 SNAPSHOT OF CSE'S WORK ON ANTIBIOTIC USE IN FOOD-ANIMAL AND AGRICULTURAL PRODUCTION SYSTEMS

A. ETHNOVETERINARY MEDICINES IN THE INDIAN DAIRY SECTOR



FOOD / INVESTIGATION

RELATED STORY

BACK TO CONTENT

OUR DAILY DOSE OF ANTIBIOTICS

As dairy farmers inject antibiotics in their livestock, chances are high that these are passed on to humans through milk, finds Delhi-based non-profit Centre for Science and Environment

RAJESHWARI SINHA, DIVYA KHATTER and **AMIT KHURANA**

Most farmers CSE spoke to did not know they must wait after an antibiotic is given to an animal before its milk is sold

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Assessment on antibiotic misuse in Indian dairy sector, 2020

Ethnoveterinary medicines have a cure rate of more than 80 per cent, shows an analysis by Centre for Science and Environment

EASY TO SWITCH

Low-cost ethnoveterinary medicines can help curb the use of antibiotics in Indian dairy sector and combat the overlooked pandemic of antimicrobial resistance

DEEPAK BHATI, RAJESHWARI SINHA AND **AMIT KHURANA**

NEW DELHI

SOME LIFESAVING solutions are so simple and obvious that they remain hidden in plain sight. This is particularly true for livestock disease treatments that have evolved over generations through experiences of communities, withstood the test of time, are embodied in local culture and practices and yet, the knowledge remains untapped in the absence of standardisation and scientific validation. More often than not, dairy farmers, and some field veterinarians, indiscriminately use antibiotics for treating even common infections in animals.

Researchers with Delhi-based Centre for Science and Environment (CSE) found evidence of such rampant misuse and overuse of antibiotics in 2020 and 2021, during consultations with dairy farmers and experts from various sectors such as animal husbandry, food safety, human health. They had observed that most dairy farmers skip the critical withdrawal period—a prescribed number of days during which the treated animal should be excluded from the milk supply chain to allow antibiotic residues to be excreted out of its body. In 2018, the Food Safety and Standards Authority of India (FSSAI) had also found antibiotic residues in milk samples.

Such abuse of antibiotics not only adds to the treatment costs, but also increases the burden of antimicrobial resistance (AMR). Interaction between antibiotic residues and pathogens in various environmental matrices (soil and water) and in living organisms can lead to formation and spread of bacteria that are resistant to antibiotics. A

PHOTOGRAPHS: THE UNIVERSITY OF TRANS-DISCIPLINARY HEALTH SCIENCES AND TECHNOLOGY, BENGALURU

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Assessment on use of ethnoveterinary medicines in the Indian dairy sector, 2022

Rationale: To understand the impact of use of ethnoveterinary medicines (EVM) on reducing antibiotic use in the Indian dairy sector.

The focus was Mastitis Control Popularization Programme (MCPP) of India's National Dairy Development Board (NDDB), which began in 2014. The University of Trans-Disciplinary Health Sciences and Technology (TDU), Karnataka, supported NDDB technically.

Key findings:

CSE analyses of NDDB's data from 25 milk unions and producer companies in 2016–October 2022 showed that NDDB was successfully able to treat about 7.8 lakh cases of disease with an 80.4 per cent cure rate.[3]

- Nine diseases in the dairy sector accounted for 6.28 lakh of these cases—mastitis, fever, diarrhoea, indigestion, wound, bloat, lumpy skin disease, prolapse, retention of placenta—that were otherwise treated with antibiotics.

- EVM application showed an overall cure rate of 80.9 per cent in these nine diseases. Of the nine, mastitis alone accounted for 2.5 lakh cases that could be treated with EVM with a 78.4 per cent cure rate (see *Table 3: CSE analysis of NDDB data*).

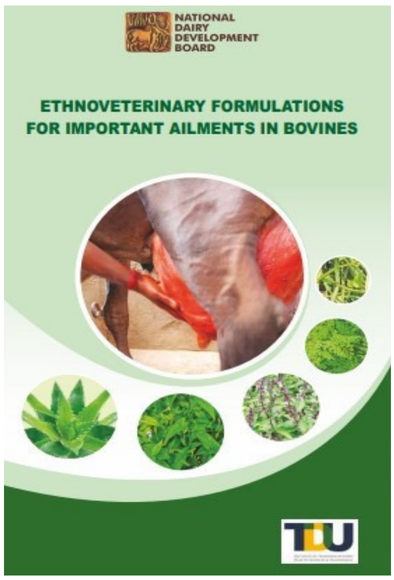
Awareness is being created through a detailed information brochure on ethnoveterinary formulations for more than 20 bovine ailments jointly developed by NDDB-TDU, available in

Table 3: CSE analysis of NDDB data

Disease	Number of unions/ producer companies treating with EVM	Total number of cases treated across unions (in '000s)	Cure rate (%)
Mastitis	25	255	78.4
Fever	18	163	82.2
Diarrhoea	20	151	84.4
Indigestion	19	32	83.4
Wound	16	9	80.5
Bloat	18	7	76.0
Retention of placenta	17	6	71.2
Lumpy skin disease	8	3	66.2
Prolapse	17	2	69.6
Subtotal		628	80.9
Other ailments		152	78.3
Total	25	780	80.4

Four key diseases covering 77% (6.01 lakh) of total cases

Nine key diseases that are treated with antibiotics



Information brochure on ethnoveterinary formulations

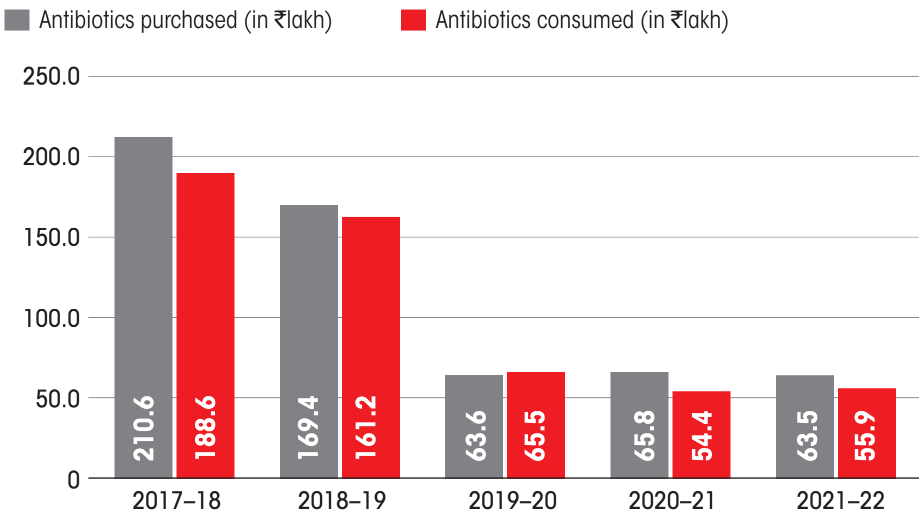
12 major Indian languages (see *photo: Information brochure on ethnoveterinary formulations*). Awareness is also generated through social media and development of an android mobile application E-Gopala jointly by NDDB -Department of Animal Husbandry and Dairying (DAHD). About 575 demonstration plots were established and 260 core group of veterinarians from 34 milk unions and producer companies were trained. MCPP is monitored through the Animal Health Management Information System.

Packaged EVM products are also sold by some milk unions to ensure continuous supply. The Malabar Milk Union in Kerala has launched a startup, Ethnovet MILMA, and are selling eight licensed EVM products.

The use of EVM led to reduced antibiotic use. This, in turn, ensured availability of safe milk and milk products for the consumer. There is reduction in overall treatment expenses as well as veterinary visits. Farmer dependence on veterinarians has reduced and their livelihoods improved as there is reduction in loss of milk productivity and lesser rejection of milk (see *Graph 2: Reduction in investment on purchase of antibiotics in 2017–22 by Sabar Dairy, a milk union in Gujarat* and *Graph 3: Reduction in veterinary visits in 2017–21 at Sabar Dairy in Gujarat*).

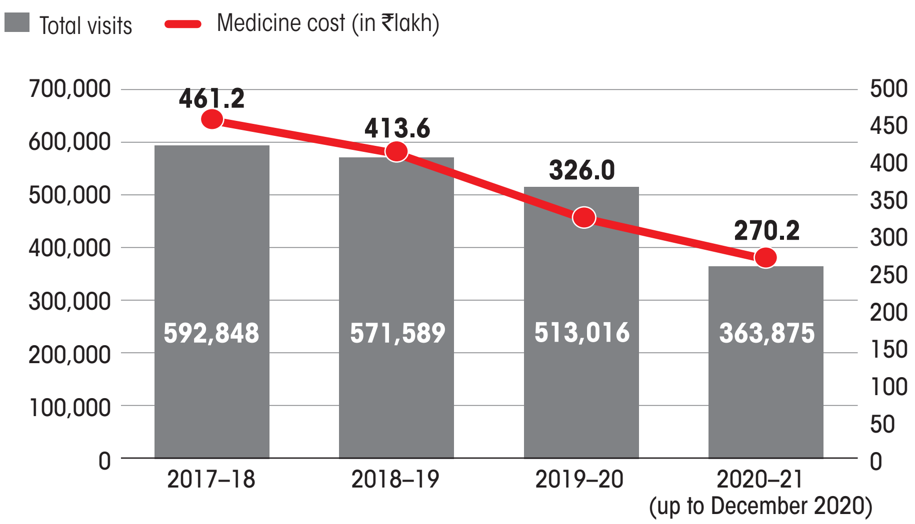
The Government of India is also promoting EVM in the Indian dairy sector. In 2021, an MoU was signed between the Department of Animal Husbandry and Dairying (DAHD), Government of India, and the Ministry of AYUSH, Government of India, to introduce the concept of Ayurveda and its allied disciplines into veterinary science.[4] *A committee was also constituted in the Department to develop a curriculum on Pashu Ayurveda/Veterinary Ayurveda and EVM to introduce in B.V.Sc and A.H. curriculum as an integrative curriculum to understand the concepts and its applications on animal health. The DAHD also advised use of herbal formulations in treatment of lumpy skin disease (LSD).*

Graph 2: Reduction in investment on purchase of antibiotics in 2017–22 by Sabar Dairy, a milk union in Gujarat



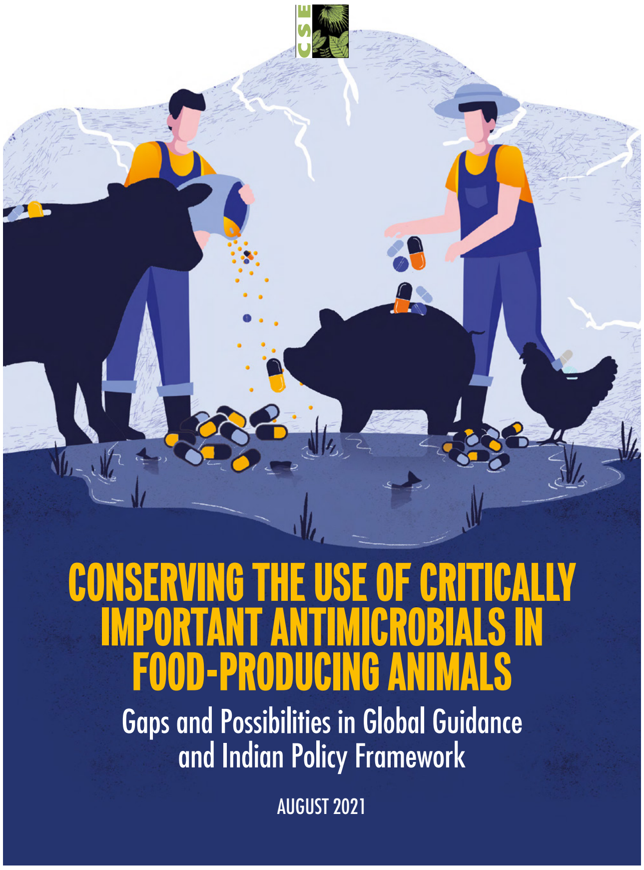
Source: National Dairy Development Board.

Graph 3: Reduction in veterinary visits in 2017–21 at Sabar Dairy in Gujarat



Source: National Dairy Development Board.

B. INCOHERENCE IN GLOBAL GUIDANCE ON ANTIBIOTIC USE IN FOOD-PRODUCING ANIMALS



Report on conserving the use of CIAs in food-producing animals, 2021

Rationale: With a weak pipeline of future antibiotics, there is need to conserve critically important antimicrobials (CIAs) for humans. CSE in 2021 analysed the global guidance in view of CIA use in food-animal production as it was creating confusion at the national level. The concerned key organizations were the World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO) and World Organization for Animal Health (WOAH) (earlier known as OIE).

Key findings:[5]

- There is a significant overlap in antimicrobials considered critical and important for humans and animals.
- There was incoherence in position on use of CIAs in food-producing animals (see *Table 4: Incoherence in global guidance on use of CIAs in food-producing animals*).
- There is need for clarity and strong action on use of antimicrobials for disease prevention in food-producing animals

Table 4: Incoherence in global guidance on use of CIAs in food-producing animals

	WHO	OIE	FAO	IACG
Highest Priority Critically Important Antimicrobials (Quinolones and fluoroquinolones, 3rd- and 4th-generation cephalosporins and colistin)				
Growth promotion	Should not be used	Should not be used	Should not be used	Should not be used
Prevention	Should not be used	Should not be used	Should not be used	Could be used
Control	Should not be used	Could be used	Should not be used	Could be used
Treatment	Should not be used	Could be used	Should not be used	Could be used
Highest priority critically important antimicrobials Macrolides and ketolides, polymixins other than colistin, glycopeptides and lipoglycopeptides, 5th-generation cephalosporins				
Growth promotion	Should not be used	Should not be used	Should not be used	Should not be used
Prevention	Should not be used	Could be used	Should not be used	Could be used***
Control	Should not be used	Could be used	Should not be used	Could be used
Treatment	Should not be used	Could be used	Should not be used	Could be used
Critically Important Antimicrobials other than Highest Priority Critically Important Antimicrobials				
Growth promotion	Should not be used	Should not be used*	Should not be used	Should not be used
Prevention	Should not be used	Could be used	Should not be used	Could be used
Control	Should not be used	Could be used	Could be used**	Could be used
Treatment	Could be used	Could be used	Could be used	Could be used

Note: For simplicity, words used here are: 'should not be used' and 'could be used'. The red text highlights incoherence.
*Could be used if there are no specific restrictions is mentioned in the OIE list, or if risk is low upon formal risk analysis;

** under exception circumstances;

*** in the absence of any recommendation, it is represented the way it would likely be interpreted by member states/ stakeholders

The study also included assessment of CIA use in the Indian poultry, dairy and aquaculture sectors as well as identified policy gaps. It provided detailed recommendations for action at the national and global level. In particular, the issue of incoherence in global guidance was discussed with concerned stakeholders and pushed for change. There are some positive developments in this regard.

C. ANTIBIOTIC USE IN CROPS

Rationale: To understand if antibiotics were also used on crops as pesticides.

To do this, CSE researchers in 2019 visited agriculture farms in Delhi, Haryana and Punjab and engaged with fruit growers in Maharashtra, Andhra Pradesh and Himachal Pradesh.

Key findings:[6]
Antibiotics were used in crops. Farmers typically sprayed two antibiotics (streptomycin and tetracycline as a 90:10 formulation) on a variety of crops, including vegetables, fruits and cereals as a preventive measure with no disease signs. Dosage and frequency of antibiotics being used were higher than what was recommended by the Central Insecticides Board and Registration Committee (CIBRC). They were also used on crops not recommended by the CIBRC (see *Table 5: Use of streptocycline in large number of approved and unapproved crops*). Being unable to differentiate bacterial and fungal infections, farmers generally mixed antibiotic with fungicides.

CIBRC had registered antibiotics as fungicides and companies were marketing antibiotics as fungicides. The recommendations of several state agricultural departments and universities were not aligned with recommendations of CIBRC.

Table 5: Use of streptocycline in large number of approved and unapproved crops

	Recommended use on crops and for disease	Used but not recommended by CIBRC	Not recommended by CIBRC but by KVK*
Vegetables	Bean (halo blight) Potato (blackleg and soft rot, bangle disease of potato) Tea (blister blight) Tobacco (wildfire) Tomato (bacterial leaf spot)	Apple gourd Bottle gourd Brinjal Cabbage Carrot Cauliflower Chenopodium Chilli Coriander Cucumber Fenugreek Garlic Gram Ladyfinger Onion Radish Spinach	Betel vine Brinjal Cabbage Cauliflower Onion Ginger
Fruits	Apple (fire blight) Citrus (citrus canker)	Grape Mango Pomegranate	Banana Mango Pomegranate Watermelon
Grains	Paddy (bacterial leaf blight)	Mustard	Gram Sesame

Source: Central Insecticide Board and Registration Committee; * Krishi Vigyan Kendra

Streptomycin is used as the second line in tuberculosis and also in pediatric patients. CSE had pushed for a regulation to prohibit its use along with several other policy changes to reduce antibiotic misuse in crops.

In 2021, a notification to ban the use of streptomycin and tetracycline in agriculture starting January 2024 was issued. It is understood that data collection is under process to inform regulatory decisions.

D. ANTIBIOTIC MISUSE IN MEAT SUPPLY CHAINS OF FAST-FOOD COMPANIES

Report on double standards of fast food companies on antibiotic misuse in chicken-meat supply chain, 2017

Rationale: Responding to the growing consumer and investor pressure, several foreign multinational companies (MNCs) publicly committed to reduce antibiotics in their chicken meat supply chains in the US, but there were no such announcements from their Indian counterparts. The assessment was done to understand their policies and plans in this regard.

CSE QUERIES TO FAST-FOOD COMPANIES

1. Does your organization have any India-specific policy for use or sourcing of your food products such as fish, meat and/or chicken raised using antibiotics? If yes, please share the details.

2. If there is no policy initiative, what is the plan in future?

3. What is the policy of your organization to test for the presence of resistant bacteria and antibiotic residues in meat or fish products sold at your outlets?

To do this, in 2017, CSE reached out to 14 key brands in India, including 11 multinational brands managed by nine companies, most of which were Indian counterparts of US-based global giants. These include Subway, Burger King, Domino's Pizza, Dunkin' Donuts, McDonald's, Pizza Hut, KFC, Taco Bell, Chili's Grill & Bar, Starbucks and Wendy's. There were three Indian brands from Café Coffee Day, Nirula's and Barista.

Key findings[7,8]

- The multinational companies operating in India did not have any India-specific commitments to eliminate misuse of antibiotics in their meat-supply chains.

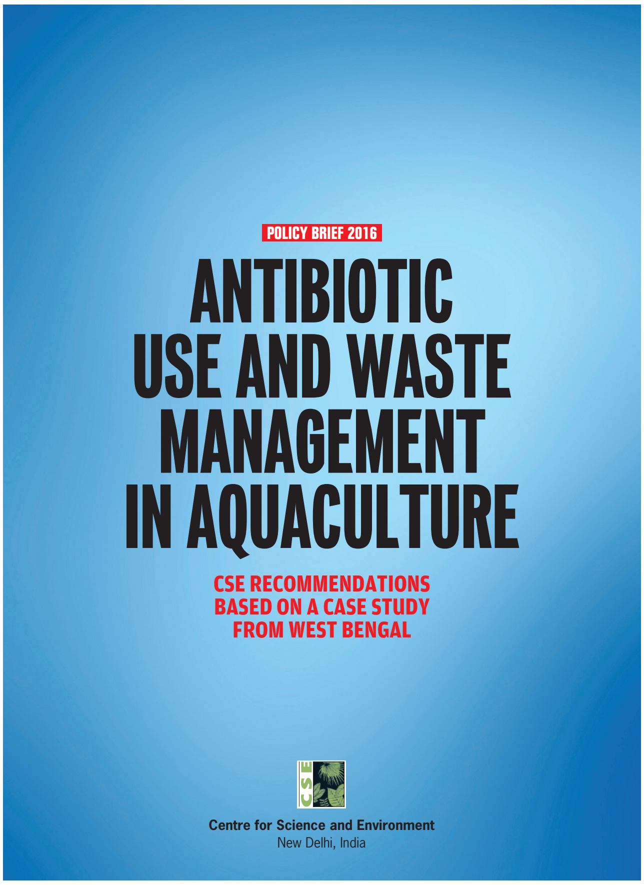
- 'Double standards' of the Indian fast-food industry were highlighted towards addressing antibiotic use in their meat supply chains.

Immediately after the study, Jubilant FoodWorks Ltd. (JFL), which had the franchise for Domino's Pizza and Dunkin' Donuts, came up with a policy on 'Usage of Antibiotics in Poultry Birds Health Management'.[9] *The policy focused on eliminating antibiotic misuse in their chicken supply chain in three phases. It committed to eliminate non-therapeutic antibiotic use by 2018, highest-priority CIA use by 2019, and limit CIA use to the second line of treatment in birds by 2020–21.*

In 2019, CSE revisited most of these companies to understand if there are more positive changes but it was not the case. In recent years, stakeholder interactions suggest that the poultry industry is more sensitized and aware about the AMR issue and is looking for solutions.

CSE is currently assessing JFL's 2017 antibiotic usage policy, which JFL claimed was on track. As in December 2023, JFL claimed to have successfully implemented its three phases and moved to the next phase of its 'No Antibiotics Ever' (NAE) policy.[10]

E. PRACTISE OF ANTIBIOTIC USE IN THE INDIAN AQUACULTURE SECTOR



Report on antibiotic use and waste management in aquaculture, 2016

Rationale: To understand antibiotic use practice and waste management practices in the aquaculture sector through a case study of West Bengal, a leading fish-producing state in India.

In 2016, CSE visited 22 freshwater and brackish-water farms and hatcheries across six key fish producing districts in the state.

Key findings:[11]
Antibiotic use was a common practice across freshwater farms, brackish-water farms as well as hatcheries. Regulatory gaps were also highlighted as, for example, the unregulated and easy availability of antibiotics, fishery-science professionals not authorized to prescribe medicines, and farmers relying largely on peers, quacks, company representatives and self-discretion. There were also inconsistencies in recommending antibiotic use in training handbooks and pamphlets.

Aquaculture wastewater without adequate treatment was being discharged into canals from which the water was sourced, reused in broodstock ponds, released into agricultural fields or let out in sewage drains. There were no specific effluent standards for aquaculture farm waste.

Freshwater aquaculture was unregulated while there was greater focus on export-oriented coastal aquaculture (brackish-water culture) through the Coastal Aquaculture Authority (CAA). The CAA guidelines prohibit use of a specific set of antimicrobials in coastal aquaculture. The Marine Products Export Development Authority (MPEDA) also implements residue-control measures in aquaculture products through the National Residue Control Plan (NRCP) and the Pre-Harvest Testing.

Subsequently, standards for antibiotic residues in meat from fish were formulated. There is greater awareness among stakeholders and there are efforts to promote the sector through technologies such as the Biofloc technology and Recirculatory Aquaculture System, which can prevent the occurrence of disease, foster better *water management and thereby help reduce antibiotic use in aquaculture.*

Biofloc technology (BFT) enables continuous recycling and reuse of nutrients within a culture medium, facilitated by minimal water exchange. BFT works on the principle of generation of the nitrogen cycle through the maintenance of high carbon-to-nitrogen (C:N) ratio. Organic matter such as uneaten feed, faeces and other waste materials are converted into microbial biomass, forming dense aggregates known as bioflocs. Bioflocs comprise a diverse blend of suspended particles and a variety of microorganisms, bound together by extracellular polymeric substances and makes protein-rich live feed. BFT aid in reducing the need for antibiotics and AMR by mitigating disease risks and managing waste through the efficient cleaning and recycling of water. It reduces the chance of infection by an inbuilt aeration system, mechanical filtration and microbial activity (biofloc defence) that compete with infectious pathogens from resources, limiting their growth and proliferation. BFT systems typically utilize aeration to maintain adequate dissolved oxygen levels and promote microbial activity.

Recirculatory Aquaculture Systems (RAS) are closed-loop systems that continuously recycle and treat water within the system, minimizing water consumption and waste discharge. Water from the culture tanks is mechanically filtered to remove solid waste particles, and then undergoes biological filtration to convert ammonia and other nitrogenous compounds into less harmful substances. It reduces need for antibiotics and the risk of AMR by its automated set-up of culture tanks with both mechanical and biological filtration units, and effectively prevents the entry of pathogens from external sources. It requires the minimal interventions to assess the culture, water and disease monitoring, which allows for greater control over the fish-farming environment, leading to improved biosecurity. It also reduces the reliance on antibiotics by mitigating the risk of fish stress by minimizing fluctuations in environmental conditions and early detection of diseases through easier monitoring of water quality and tank conditions. RAS systems require significant initial investment and operational costs, but offer advantages such as higher seed survival rate, reduced environmental impact, lower water usage, and the potential for year-round production regardless of external conditions.

F. ANTIBIOTIC USE IN THE INDIAN POULTRY SECTOR

Assessment on antibiotic residues in chicken meat and antibiotic misuse in Indian poultry sector, 2014

Rationale: To understand the level of antibiotic use in the poultry sector. In addition to the field survey, it also involved a laboratory study on antibiotic residues in chicken meat.

In 2014, CSE tested 70 chicken samples sold in retail outlets in Delhi-National Capital Region (NCR) for the presence of six antibiotics, oxytetracycline, chlortetracycline, doxycycline, enrofloxacin, ciprofloxacin and neomycin. It further understood the practice of raising poultry in the nearby state of Haryana, from where meat was supplied to Delhi-NCR.

Key findings:[12]
It was found that 40 per cent of all samples contained antibiotics. Except neomycin, residues of five antibiotics were detected in chicken samples.

From the ground, it was clear that antibiotic use was considered an easy and economical solution for high profitability. Antibiotics were given to day-old chicks at broiler farms. Use of antibiotic growth promoters (AGPs) was integral to broiler farming as antibiotic-laden feed. Routine preventive administration of antibiotics was also a common practice due to their easy availability. Farmers generally did not follow withdrawal periods and veterinarians had a limited role in non-therapeutic antibiotic administration. Veterinarians, influenced by incentives from pharmaceutical companies, prescribed antibiotics liberally.

While small and medium farms heavily relied on antibiotics to attain a favourable feed conversion ratio (FCR), bigger farmers, despite being more aware and resourceful, were far from practising good farm-management measures.

In a follow-up assessment of 2020, CSE again highlighted the need for regulating chicken feed.[13]

The study of 2014 paved the way for the Indian standards for antibiotic residues in the poultry meat. Advisories went from the concerned departments to check antibiotics as growth promoters in feed. In 2019, colistin was banned for use in food-animal production. It also led to the formulation of standards for chicken feed by the Bureau of Indian Standards recently.

Consumers are more aware and demand antibiotic-free milk and meat, and there are players in the market who claim to be selling antibiotic-free products.

G. ANTIBIOTICS IN HONEY

Assessment on antibiotic residues in honey samples and antibiotic misuse in Indian apiculture, 2010

Rationale: Against the backdrop of no standards for antibiotics in honey sold domestically, honey was tested in 2010 to assess antibiotic use in apiculture and residues.

Key findings:[14]
Multiple antibiotics in 11 of the 12 honey samples tested were found. Six antibiotics, oxytetracycline, chloramphenicol, ampicilin, enrofloxacin, ciprofloxacin and erythromycin, were tested.

In 2014, the mandatory standards for ten antibiotics in honey were notified.

4

MANAGING ENVIRONMENTAL AMR SPREAD

MANAGING ENVIRONMENTAL AMR SPREAD

4.1 CHALLENGES

- **Environment aspects of AMR have received the least attention so far** from concerned global agencies as well as national governments, which has led to a limited action so far. Reasons include cross-cutting and the complex nature of the problem; limited understanding on solutions that could be implemented easily; perception of limited tangible gains in the short term; resource constraints to manage waste; and apportioning of blame among different sectors within the environment space and outside of it.

- **The scientific community is developing evidence but consensus on whether it is enough to act is not always easy to arrive at.** Moreover, understanding on emergence, spread and transmission dynamics, and role of sewage treatment plants and effluent treatment technologies to contain AMR is still developing.

- **Antibiotic manufacturing discharges is the main focus**, while healthcare delivery, agriculture and food chain and pharmaceutical manufacturing are considered three economic-sector value chains that can impact AMR. Managing antibiotic manufacturing discharges has huge challenges such as the impact it may have on affordable access to antibiotics in LMICs. While the pharmaceutical industry feels unduly targeted, WASH and AMR linkages and farm waste await required attention.

- **Containing AMR in waste is scientifically challenging**. Industrial waste management is expensive and cost-effective solutions are hard to find. Moreover, AMR is a different subject for environmental regulators, who are otherwise trained and equipped to handle industrial pollutants like heavy metals and agriculture chemicals such as pesticides.

- **Over-emphasis on environmental surveillance,** which is complex, instead of focusing on simple and cost-effective waste-management and preventive technologies.

- **Environment as a triple challenge can make it more complex.** Addressing environmental aspects as part of triple challenge of AMR, biodiversity and climate change can further make the connections less visible and action more complex and delayed.

4.2 POSSIBILITIES

- **Environment agenda is largely about waste management at the hotspots**, which may vary across countries. LMICs may have to prioritize waste management at point sources over surveillance efforts across, for example, non-point sources. They will also have to prioritize key sectors and hotspots. For example, LMICs with a big antibiotic manufacturing sector will have to design and promote solutions accordingly as against others with a large aquaculture sector or a large dairy sector.

- **Prevention should be integral to the waste management agenda in LMICs**. For example, adopting process-control measures in antibiotic manufacturing is a more effective approach than expensive end-of-pipe treatments. Similarly, less antibiotic use in farms is a better approach than spending excessively on detecting and mitigating AMR determinants in waste.

- **Managing waste coupled with resource conservation will get due attention**. Waste from dairy farms can be converted to biogas. The slurry or the waste can also be used as a fertilizer for agriculture. Both can lead to greenhouse gas (GHG) emission reductions, thereby calling for greater private investments and incentives from governments. Before applying to fields, it should be made AMR-safe though. Additionally, national guidelines on land application of manure are needed.

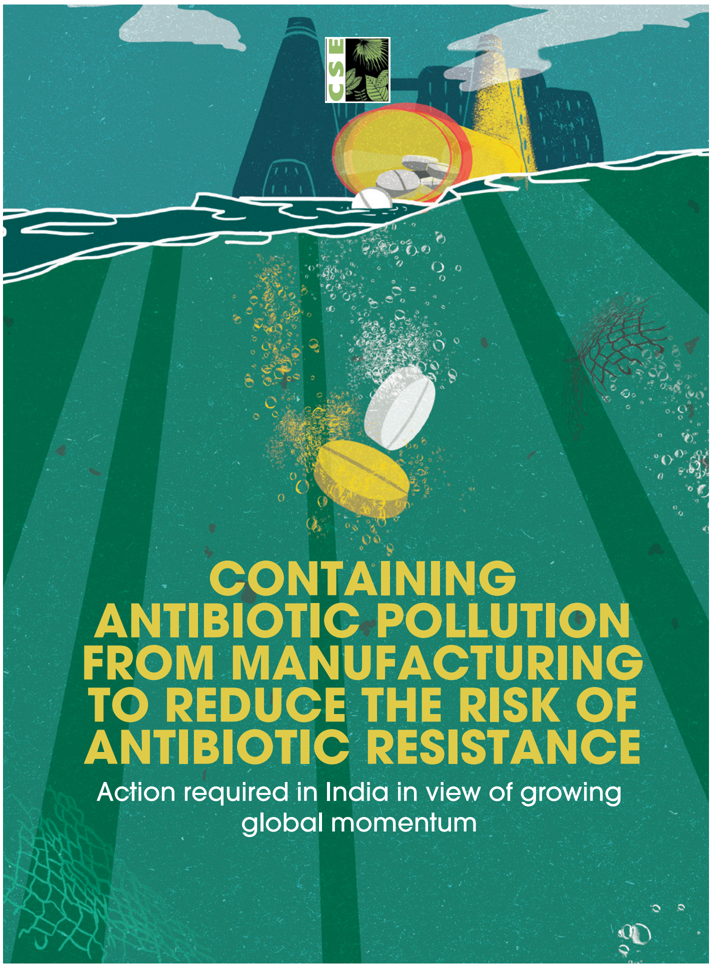
- **Low-cost yet effective waste-management technologies are the need of the hour**. Be it for antibiotic residues or metabolites, resistant bacteria or genes conferring resistance, technologies to manage these AMR determinants in different waste streams are critical. These should be developed, promoted and incentivized specific to waste types.

- **Global guidance on effective waste management from key contributing sectors is missing**. Most environment standards and waste management approaches at the national level are also not AMR-specific. Further, there are so far no standards for antibiotics in manufacturing discharge in any country.

- **Secured political will for long-term action will need a better case on co-benefits and overall gains**. For example, understanding the actual cost/impact of food that is produced in intensive farms—which can cause zoonoses, AMR, pandemics, loss of biodiversity, loss of water and land to grow feed for animals—can help invest in a holistic long-term corrective action such as one that can address the triple challenge of AMR, biodiversity and climate change.

4.3 SNAPSHOT OF CSE'S WORK ON ANTIBIOTIC POLLUTION FROM MANUFACTURING AND DISPOSAL

A. CONTAINING ANTIBIOTIC POLLUTION FROM MANUFACTURING



Report on containing antibiotic pollution from pharmaceutical manufacturing, 2023

Rationale: India has a big pharmaceutical manufacturing industry, which ranked third globally in production during 2022–23 and is an important part of the global antibiotic supply chain.

In view of growing global momentum of containing antibiotic pollution from manufacturing, CSE conducted in 2022–23 a study to understand waste-management practices of antibiotic manufacture and pollution-control strategies of regulators. The study involved a survey with 14 big and small active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) manufacturers (four large and 10 small and medium scale) and interacting with several stakeholders and regulators at the national and state levels.

Key findings:[15]
The report presented a detailed account of:

- Antibiotic manufacturing hubs and associated network of common effluent treatment plants (CETPs) in India;
- India's role in the global antibiotic supply chain and the scale of import and export of antibiotic pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs);
- India's policy framework and systems in place to contain pharmaceutical pollution;
- Select case studies of CETPs;
- Results of a survey with big and small API and FPP manufacturers on their waste management practices; and
- Available technology options to mitigate antibiotic pollution.

It suggests that:
- The consensus to act on manufacturing discharge is growing globally;
- There are huge expectations from the Indian pharmaceutical industry;
- There are no standards to directly address antibiotics in manufacturing discharge;
- The antibiotic limits proposed in the draft Indian standard are yet to be notified;
- Pharmaceutical companies adopt a varying set of waste

management approaches based on several factors;
- Most CETPs in antibiotic hubs rely on conventional treatment approaches; and
- Waste-management approaches are best when adopted on the basis of specific factors of a company/CETP.

A set of recommendations were outlined:

National and state government ministries/departments, regulatory agencies, scientific and academic institutes should:
- Invest in creating awareness and building the capacity of stakeholders involved;
- Develop data to support policy formulation, implementation and monitoring;
- Formulate and implement a long-term research agenda;
- Carry out regular surveillance and monitoring of manufacturing units and CETPs;
- Strengthen laboratory capacity to support surveillance efforts;
- Notify legal limits for antibiotics in discharge from manufacturing units and CETPs;
- Upgrade and enable capacity and capability of CETPs to address antibiotics; and
- Support small- and medium-scale companies in managing antibiotic discharges.

The antibiotic manufacturing (API/FPP) industry in India should:
- Focus and invest on process-control measures, which are like prevention;
- Build in-house capacity and upgrade waste treatment systems aimed at eliminating antibiotics in manufacturing discharge; and
- Support surveillance, policy-making and sharing of data.

Subsequently, the findings were discussed with stakeholders and it is clear that:
- A strong need is felt to contain antibiotic pollution from manufacturing. The limits for antibiotics in discharge can be developed while adopting a right balance between

industry concerns, regulator capacity as well as public and environmental health needs.
- The general sense is that some technologies to degrade antibiotics are available and can be upscaled with due considerations. Big industry relies on Zero Liquid Discharge, which if done right can be useful to limit antibiotic pollution. Small industry can rely on CETPs, which can be upgraded after assessment.
- Most importantly, certain state pollution control boards and stakeholders have proactively adopted measures and best practices. There are CETPs that can show the way to successfully handle antibiotics in waste.

B. DISPOSAL OF UNUSED ANTIBIOTICS

Rationale: Improper disposal of unused and expired antibiotics in households are a potential waste pathway for AMR. In India, there are laws and guidelines on how expired drugs at the household level should be discarded.

In order to understand the practice, this study was conducted in 2019. It involved a survey and interaction with stakeholders in and around Delhi-NCR and in Kerala.

Key findings:[16]
Drugs which are unused or expired at the household levels are often disposed of improperly. They are discarded into drains or along with regular municipal waste. Similarly, some retailers also dispose of them into open drains/nallahs, bury or dump underground or burn them.

CSE also highlighted the role of drug take-back initiatives which ensure the return of unwanted drugs, including expired and unused drugs, from their point of generation to a facility for their appropriate disposal. Key elements of a drug take-back approach involves collection of unwanted drugs from households, their sorting, and transportation to disposal facilities. Several EU countries have adopted such take-back programmes.

In India, a similar drug take-back initiative, called the Programme on Removal of Unused Drugs (PROUD), has been implemented in the state of Kerala. PROUD was piloted in 2019 in Thiruvananthapuram district with collaboration of the Drug Control Department, Kerala and the All-Kerala Chemists and Druggists Association. About 200–300 locked collection boxes were placed near select pharmacies, bus terminals and markets where people were encouraged to deposit unused pharmaceutical products. The waste was then sent to a common biomedical waste-treatment facility in a neighbouring state, Karnataka, for incineration. The programme collected about 15 tonnes of drugs in the first year. The costs incurred were dependent on the volume of drugs collected periodically (see *photo: Drug-collection box placed outside a pharmacy store in Thiruvananthapuram district of Kerala as part of the PROUD programme*).

Operation of the programme saw loss of momentum due to change of leadership at the departmental level as well as the state level. PROUD is currently under discussion for being revived again under a ‘public–private partnership’ model.

Drug-collection box placed outside a pharmacy store in Thiruvananthapuram district of Kerala as part of the PROUD programme

5

IMPLEMENTING NATIONAL ACTION PLANS EFFECTIVELY

IMPLEMENTING NATIONAL ACTION PLANS EFFECTIVELY

5.1 CHALLENGES

- **The first phase of multi-sectoral AMR national action plans (NAPs) received limited success on the ground**, particularly in LMICs. Reasons include:
  - o Limited political will in the backdrop of competing priorities;
  - o Inadequate domestic financial resources;
  - o International funding support is limited and often not aligned with local needs;
  - o NAPs are driven largely by human-health stakeholders with limited ownership from animal and environment sector stakeholders;
  - o Limited know-how and capacity, specifically in non-human sectors;
  - o A big to-do list developed without much-needed prioritization;
  - o Local context not really integrated into planned actions;
  - o Over-emphasis on aspects like resource-intensive integrated surveillance that jeopardized action on simple, implementable prevention-based solutions;
  - o Limited estimates of cost of action and inaction at the national and sectoral level; and
  - o In some countries such as India, the responsibility for planning and implementing action shifts to more stakeholders in the states/provinces.

- **It remains to be seen if learnings are being applied in developing the second phase of NAPs.** There are discussions about prioritized, better-informed, sector-specific plans. Sector-specific surveillance is also gaining more attention than integrated surveillance. Competing priorities of nations are not expected to change much, but the situation on financing and political will must become favourable for effective national action.

- **Baseline understanding to plan and reduce antibiotic use is missing.** Several LMICs have committed to antibiotic reduction targets in food-animals and humans as part of the Muscat Manifesto 2023, but the roadmap to meet those commitments needs a baseline understanding and is to be aligned with the second phase of NAPs.

- **Gap in global guidance and national understanding.** For example, there is greater focus on 'prevention' at the global level but how it gets integrated into sectoral action at the national level remains to be seen. Environment and waste seem to be better understood in some countries, but global guidance on how to go about it is limited and impacts action across the countries.

- **Combating AMR as part of the One-Health strategy receives a mixed response**. On the one hand, it can potentially dilute the otherwise complex problem of AMR, which warrants a dedicated attention for urgent and targeted action. On the other, the narrative of One Health brings focus on inter-connectedness of animal–human–environmental ecosystems.

5.2 POSSIBILITIES

For effective implementation of NAPs in LMICs, the following broad aspects could be considered:

- **NAPs should be prioritized** to identify select key tasks at the national, state, local and sectoral levels. Those which can be easily done, are cost-effective, have greater benefits, address urgent need, leverage existing capacity and/or offer co-benefits should be prioritized first.

- **The 'prevention' approach needs to be made integral to national action.** LMICs will struggle to bear the cost of crises or invest heavily in cleaning up.

- **Local cost-effective but impactful solutions/alternatives should be developed, promoted and incentivized**. This would reduce dependence on expensive and imported options that may also have limited local relevance. Best practices should be scaled up, if possible. The solutions need to be communicated for greater adoption.

- **Modularized approach should be considered to scale up**. Action should be designed based on available capacity and funds to build momentum. Complex but important tasks could be expanded based on pilots in select areas.

- **Sustainable financing should be the basis for NAP implementation.** Dependence on ad-hoc and short-term funding should be avoided. All efforts should be made to mobilize domestic funds.

- **A strong case for political buy-ins should be developed**. This could involve communicating the overall benefits of effective action in terms of costs, public health and societal benefits.

- **Preventing AMR should be a whole-of-society approach**. Citizens and consumers should be made part of the solution.

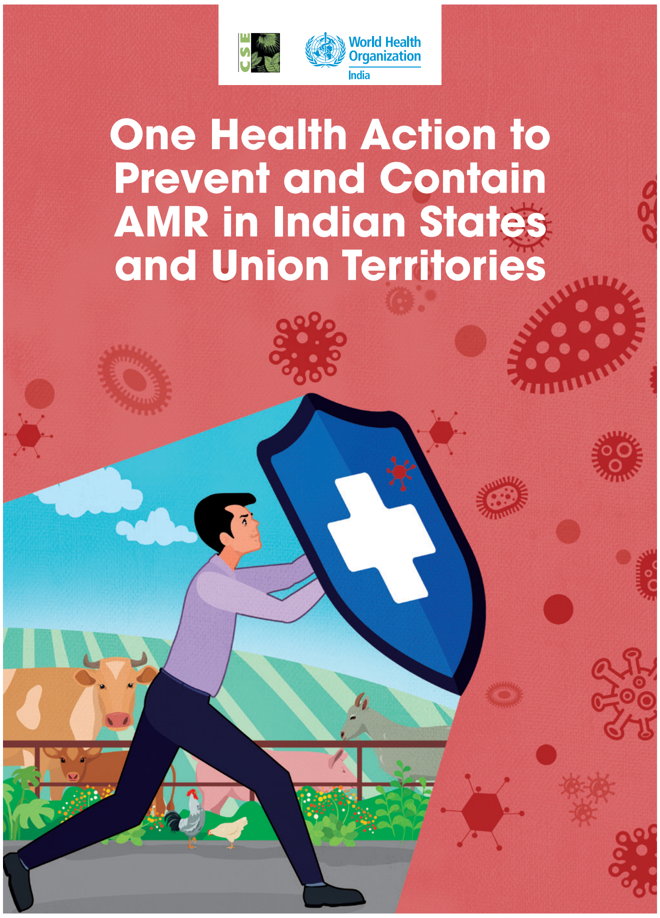
- **Simple and effective communication is the key for behaviour change**. The issue of AMR needs to reach masses as have the issues of air pollution and climate change.

- **Perception about 'waste' needs to change.** Managing waste should be prioritized.

- **Animal-sector stakeholders will have to make food systems sustainable.** They will have to make sure that more food is produced for livelihood, development and trade but without increasing the risks of AMR for local and international populations.

- **AMR should get due attention** if it is addressed as part of the larger One-Health approach.

5.3 SNAPSHOT OF CSE'S WORK IN INDIA



Report on One-Health action to prevent and contain AMR in Indian states and Union territories, 2023

Rationale: In India, effective action against AMR depends significantly on state stakeholders as human health, animal husbandry, fisheries and pollution control are managed by states and Union territories.

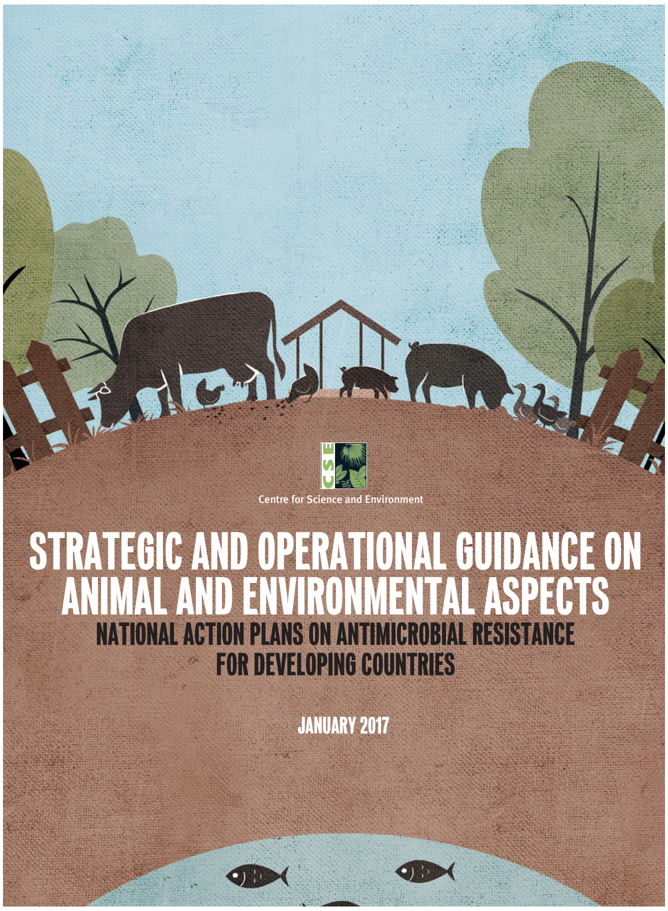
Key findings:[17]
CSE, along with WHO India, came up with a prioritized set of actions across the One-Health sectors that were discussed and agreed upon by state-level stakeholders over a series of consultations in 2022–23.

These actions are implementable and impactful across different sectors related to governance prerequisites, awareness and education, surveillance of resistance and residues, prevention and control of AMR and optimizing antibiotic use.

CSE was previously involved in the development of India's National AMR Action Plan and state action plans for Kerala, Madhya Pradesh and Delhi and contributed on aspects related to animal and environmental dimensions of AMR.

5.4. SNAPSHOT OF CSE'S GLOBAL WORK

A. GUIDANCE ON ANIMAL AND ENVIRONMENTAL ASPECTS OF NATIONAL ACTION PLANs (NAPs) OF DEVELOPING COUNTRIES



Report on strategic and operational guidance on animal and environmental aspects of AMR for developing countries, 2017

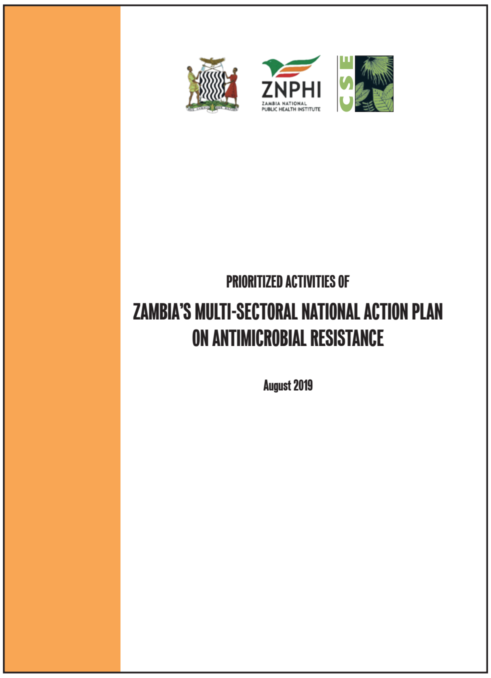
Rationale: Recognizing the challenges of the developing world, CSE developed in 2017 a strategic and operational guidance on animal and environmental aspects of AMR.

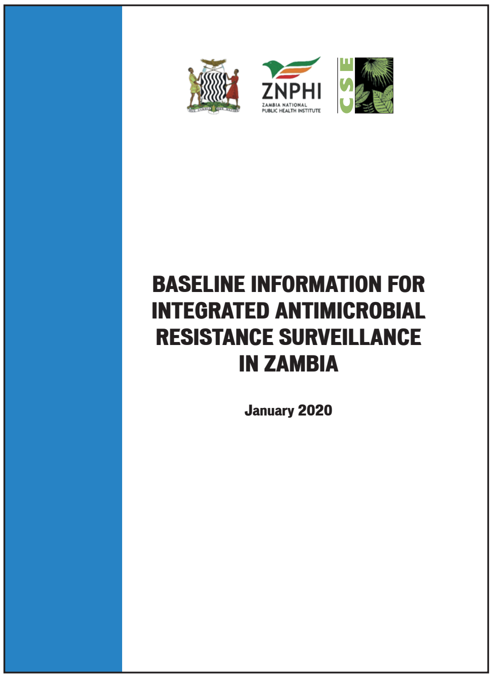
Key findings:[18]
Based on inputs from experts from both developed and developing countries, the guidance reflected key interventions that should be a part of the NAPs of developing countries to contain the emergence and spread of AMR from animals and environment sectors. These interventions were developed across key thematic areas (see *Figure 4: Framework for guidance on NAP-AMR*).

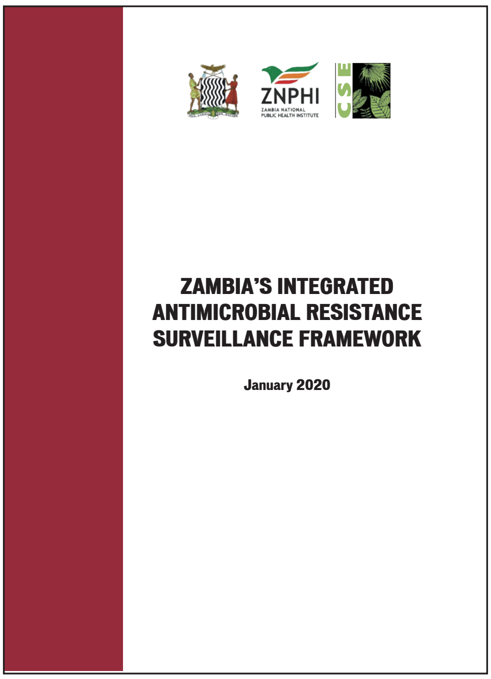
Figure 4: Framework for guidance on NAP-AMR

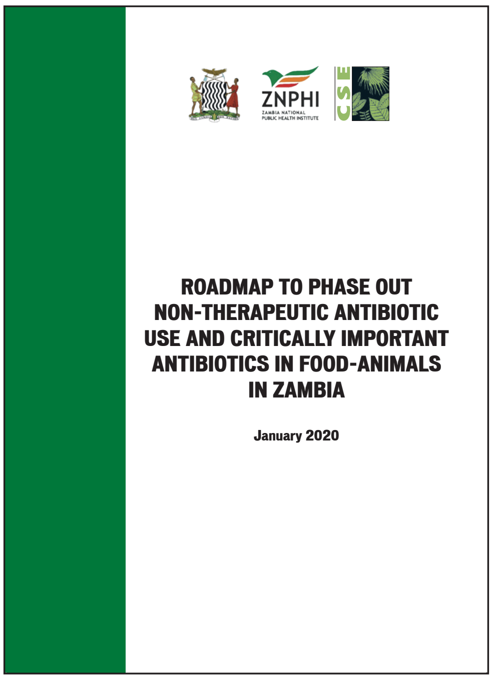
<table>
<tr><td rowspan="11">INTERVENTION AREAS</td><td rowspan="2">Policy, law, regulations, standards or programmes</td><td colspan="5">Responsible antibiotic use</td></tr>
<tr><td colspan="5">THEMATIC AREAS</td></tr>
<tr><td rowspan="2">Implementation tools such as infrastructure, capacity, systems or resources</td><td>Supply of antibiotics</td><td colspan="3">Production systems</td><td>Antibiotic use</td></tr>
<tr><td></td><td>Reduce need for antibiotics</td><td>Veterinarians and veterinary services</td><td>Antibiotic use</td><td></td></tr>
<tr><td rowspan="2">Advocacy, awareness and education, training or curriculum</td><td colspan="5">Surveillance of antibiotic use and antibiotic resistance</td></tr>
<tr><td colspan="5">THEMATIC AREAS</td></tr>
<tr><td rowspan="4">Record keeping, database generation, collation, dissemination and research or survey</td><td>Antibiotic use</td><td colspan="2">Antibiotic resistance</td><td>Antibiotic residues</td><td>Environmental surveillance</td></tr>
<tr><td colspan="5">Environment management</td></tr>
<tr><td colspan="5">THEMATIC AREAS</td></tr>
<tr><td>Registration or licensing</td><td colspan="2">Biosecurity, sanitation and hygiene or good manufacturing practices</td><td>Waste management</td><td>Research</td></tr>
<tr><td>Review, monitoring or feedback</td><td colspan="5">Short term (S): <1 yr; medium term (M): 1–3 years; long term (L): 3–5 yrs; (S-M-L): continues throughout</td></tr>
</table>

B. SUPPORTING THE IMPLEMENTATION OF THE NATIONAL ACTION PLAN OF ZAMBIA


PRIORITIZED ACTIVITIES OF
ZAMBIA'S MULTI-SECTORAL NATIONAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE
August 2019


BASELINE INFORMATION FOR INTEGRATED ANTIMICROBIAL RESISTANCE SURVEILLANCE IN ZAMBIA
January 2020


ZAMBIA'S INTEGRATED ANTIMICROBIAL RESISTANCE SURVEILLANCE FRAMEWORK
January 2020


ROADMAP TO PHASE OUT NON-THERAPEUTIC ANTIBIOTIC USE AND CRITICALLY IMPORTANT ANTIBIOTICS IN FOOD-ANIMALS IN ZAMBIA
January 2020

Reports on different aspects of the implementation of the AMR action plan in collaboration with the Ministry of Health, Zambia

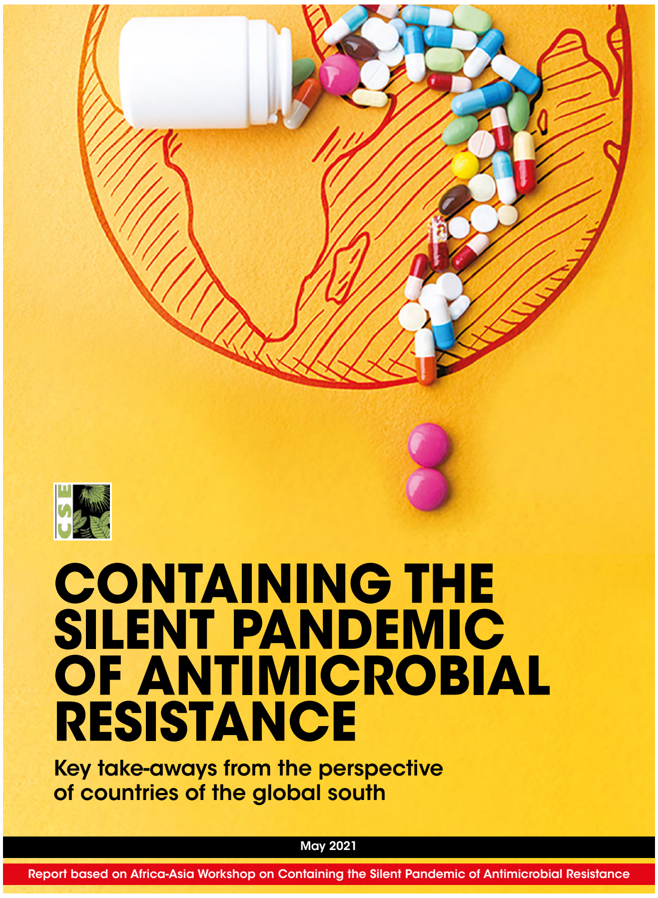
Rationale: To engage with the Zambian Ministry of Health and support implementation of their national action plan on AMR

Key findings:
During 2018–20, CSE worked with Zambian stakeholders to come up with:

- Reprioritization of Zambia's national action plan on AMR in order to make the plan more specific, targeted and achievable;[19]
- Baseline information for integrated AMR surveillance in Zambia;[20]
- Integrated AMR surveillance framework for Zambia;[21] and
- A roadmap to phase out non-therapeutic antibiotic use and CIAs in food-animals in Zambia.[22]

These outputs were also further discussed with stakeholders at the pan-Africa level.

C. CONTAINING THE SILENT PANDEMIC OF AMR FROM THE PERSPECTIVE OF COUNTRIES OF GLOBAL SOUTH



Report on containing the silent pandemic of AMR, 2021

Rationale: To identify Global South perspectives on what needs to be done to contain the silent pandemic of AMR

Key findings:[23]
The workshop brought together over 125 experts from across the world, including over 100 experts from 24 African and Asian countries. Key points that emerged include:

- Learnings from the COVID-19 pandemic response should be leveraged

- Effective implementation of AMR National Action Plans needs a whole-of-government and whole-of-society approach;

- Political commitment is critical and funding to contain AMR needs specific steps at the national, regional and global levels;

- Regarding tackling environmental AMR, the priority of LMICs should be to manage waste effectively through affordable waste management approaches at known hotspots;

- Containing AMR from food production settings (livestock, aquaculture, crops) needs a short-term approach of eliminating misuse and conserving critically important antimicrobials, and a long-term approach towards sustainable food systems;

- The role of civil society, consumers and media in containing AMR is critical. They play a catalytic role, help build positive pressure and bring credible and verifiable evidence on the table; and

- Countries expect a strong global governance mechanism to stimulate action on AMR.

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In September 2024, UN member states will discuss and commit to future action on AMR at a high-level meeting during the General Assembly in New York. Experts worldwide see this as a big opportunity for stronger global action against the global threat of AMR. Bold outcomes, specific commitments and targets are expected. With the drivers and levels of AMR varying among countries and differences in resources to fight AMR, a good understanding about what can work in LMICs will make a huge difference.

This report highlights the challenges and possibilities from the perspective of LMICs in select areas related to, for example, access to effective antibiotics, sustainable food systems, environmental AMR spread, and implementation of national AMR action plans. It is based on a decade-and-a-half-long experience of CSE's work in India and engagements with African and Asian countries as well as global stakeholders. At the core of this work is the evidence and learnings developed from the ground and a perspective that is aligned to sustainable and equitable development of the Global South.

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