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Understanding Antimicrobial Resistance
What is Antimicrobial Resistance (AMR)?

From a humble bacteria like me, you become a super bug. What's your secret?

Antibiotics!

Source: Down to Earth
What is Antimicrobial Resistance (AMR)?

- **Antimicrobial resistance** (AMR) happens when bacteria, viruses, fungi, and parasites that cause infections in us, humans, become resistant to the medicines we use to kill them. Thus, these microbes can no longer be killed and it becomes very difficult to treat our infections.

- The major problem pertains to the growing resistance among bacteria against antibiotic medicines. This is commonly known as **antibiotic resistance**.
How does AMR happen?

- Occurs **naturally over time**; accelerates by misuse and overuse of antimicrobials to treat, prevent or control infections in humans, animals and plants.

- Antibiotic use exerts **greater selection pressure** on bacteria, causing resistant ones to survive.

- At a cellular level, resistance is acquired through **transfer of genetic material** from one bacteria to another.
Scale and impact of AMR problem is huge

- **Multiple microorganisms** (bacteria, virus, fungi, parasite)
- **Different types of a bacteria** (e.g. Gram positive bacteria, Gram-negative bacteria)
- **Infections of multiple organ systems/body tissues** (gut, respiratory, urinary, blood etc.)
- **Different sources of infection** (community-acquired, hospital-acquired, food-borne)
- **Impacts outcome of infectious diseases, non-communicable diseases** (e.g. chemotherapy in cancer, diabetic foot), **post-surgical infections** (e.g. hip transplant, cardiac surgery)
- **Multi-drug resistance** in a bacteria; **Resistance against almost all antibiotics** (old antibiotics like tetracycline, penicillin; new antibiotics like 3rd, 4th, 5th generation cephalosporins; last resort like colistin)
- **Prevalent across globe, all age groups**
Estimated 10 million lives in a year at risk by 2050, if no action taken; About 90% in Asia and Africa; ~2M in India

Deaths attributable to AMR every year by 2050

- Asia: 4,730,000
- Africa: 4,150,000
- Latin America: 392,000
- Europe: 390,000
- North America: 317,000
- Oceania: 22,000

Mortality per 10,000 population
Impact beyond human health; more in low- and middle-income countries (LMICs)

**Human Health**
- Antibiotics are becoming ineffective to treat even common infections and saving lives. Treatment options reducing or becoming expensive, longer hospital stays
- **1.27 M deaths in 2019** (attributed directly); **4.95 M deaths in 2019** (associated with AMR)
- AMR killed more people than HIV/AIDS (0.86 M) or malaria (0.64 M) in 2019

**Livelihood, Economy and Development**
High-impact scenario by 2050
- **3.8% global annual GDP** lost
- **Livestock** production in LMICs would decline the most, with ~11% loss

By 2030
- Additional 24 million people into extreme poverty; most in LMICs

**AMR could derail the achievement of SDGs by 2030**
Multiple drivers of AMR

**AMR causing determinants**
- Antibiotic resistant bacteria
- Antibiotic resistance genes
- Antibiotic residues

**Use/misuse/overuse of antibiotics**

- **Food-animal production systems**
  - Poultry, fisheries, dairy, swine
  - Intensive production systems
  - Routine antibiotic use for growth promotion, disease prevention
  - Use of critically important antibiotics (CIA) for humans

- **Crop production systems**
  - Routine use of antibiotics (e.g., streptomycin) as fungicides in crops to prevent diseases

- **Human health**
  - Self medication
  - Over prescription
  - Over-the-counter sale
  - Access vs excess issue

- **Waste and Environment**
  - Point and non-point sources
  - Hotspots include waste from farms, factories, healthcare settings and sewage/water treatment plants
  - Non-point sources include rivers etc.

**AMR: a One Health concern**
Why should we be worried?
The triple crisis of AMR

- Crisis 1: Antibiotics are becoming ineffective
  - Critically important antibiotics losing power to kill bacteria (e.g., fluoroquinolones, aminoglycosides, carbapenems and cephalosporins)
  - Expensive antibiotics now needed to be used
  - Ultimately, treatment options are reducing

- Crisis 2: The antibiotic development crisis
  - Golden era for antibiotic development was during 1950-1970; no new class of antibiotics developed since 1980s, especially against Gram-negative bacteria.
  - Those developed over last decade inadequate to treat growing unmet need; growing resistance

- Crisis 3: The issue of access
Global developments to contain AMR

- Quadripartite-WHO, FAO, WOAH, UNEP
- Global Leaders Group on AMR
- United Nations General Assembly, World Health Assembly
- G7, G20
- National Action Plans; multi-sectoral action at national and subnational level
- Civil society
- Industry
- Scientific community
- Student community, Youth Ambassadors
CSE’s journey on AMR

- Access to effective antibiotics
- Sustainable food production systems
- Managing environmental AMR spread
- Implementing National Action Plans effectively

Research  Policy advocacy  Awareness  Capacity Building  Lab studies
Access to effective antibiotics

Cover story and report on the crisis of antibiotic research and development, 2023
Our new line of antibiotics are getting a very positive response.

No. From the microbes.

From the patient?

Antimicrobial resistance.
The antibiotic pipeline is weak and lacks promise

Priority pathogens, *M. tuberculosis* and *C. difficile*

297 (anti-bacterial candidates)
- 217 (preclinical)
- 77 (clinical)
- 3 (pre-registration)

32 (non-traditional)
- Agents that lack intrinsic antibacterial activity and work through other means; May not substitute traditional

45 (traditional)
- Agents that act by directly targeting components necessary for bacterial growth or to kill the pathogen

28 (target WHO priority pathogens)

In comparison:

>10,000 medicines under active clinical development for cancer

>1,800 for neuropsychiatric conditions

~1,500 for endocrine, blood and immune disorders*

Source: WHO database updated till late 2021; *WHO's Global Health Observatory on Health Research and Development;
Industry attributes to antibiotic **market failure**; venture capitalists also moved away to more profitable areas

- Out of **1007 molecules** in clinical pipeline of 15 global pharmaceuticals, **only 13 are antibacterial** candidates, being developed by **four companies**. 8 out 13 are by one company (GSK).
  - **411** candidates for cancer;
  - **150** for immunology, allergy, inflammation or respiratory diseases;
  - **84** for cardiology, metabolism or renal disease areas.

The **BIG EXODUS** is not only because of high risk low return (due to often cited market failure) but also because of profits in other areas.
Sustainable food production systems
Food from animals is produced in intensive systems driven more than ever by demands and commercial interests.
Characteristics of intensive farming systems

- Large-scale units with **high stocking density** of animals/birds/fish

- **Genetically selected similar breeds** for productivity (not disease resilience)

- Kept under **confined conditions** and in **close proximity; high stress**

- Limited focus on good animal husbandry

- **Dependence on commercial feed**, inputs (also known as animal feeding operations, factory farms)

- Often **geographically concentrated**; vertically integrated by large players; involves contract farming

- **Industrial systems** but considered agriculture; can bypass required regulatory attention
This has led to different types of antibiotic use in food systems

Antibiotic use

- **Therapeutic**
  - Therapeutic doses
  - Clinically diagnosed infectious disease

- **Non-therapeutic**
  - Increase the rate of weight gain
  - Increase efficiency of feed utilization
  - Mass, routine use (largely through feed at sub-therapeutic doses)

  - Individual or group of animals
  - With no clinical sign
  - Often routine use

  - Prevention – (control / metaphylaxis)
  - In a group of healthy animals (presumed to be infected/may have already been sub-clinically infected because they are at risk of infection), where one or more animal is already infected

Though non-therapeutic, now being positioned as therapeutic by some agencies.
Antibiotics fuel intensification which is a driver for AMR, climate change, zoonoses and pandemics.

Source: CSE analysis
CSE’s work on AMR in food systems

Residues of multiple antibiotics were found in 11 out of the 12 samples, including both international brands.

Residues of multiple antibiotics found in chicken meat; Practice of rampant non-therapeutic antibiotic use in industrial food production systems highlighted.

Antibiotic use was a common practice. Farm effluent discharged without adequate treatment into canals, agricultural fields or let out in sewage drains; regulatory gaps highlighted.

Practice of antibiotic use and misuse in Indian dairy sector highlighted; assessment of practices in milk processing units w rt detection of antibiotic residues in milk.
CSE’s work on AMR in food systems

Antibiotic misuse in the fast food supply chain; ‘Double Standards’ of global giants as no such commitments are made by these for India; revisited in 2020-story largely same except Jubilant

Antibiotics registered as fungicides; Indiscriminate use on crops; use in higher doses and frequency; streptomycin commonly used

Practice of antibiotic administration though feed in poultry sector; unregulated nature of feed leading to its misuse

On-the-ground situation in India wrt CIA use in food-animal sector-dairy sector (21 CIAs from six classes), poultry sector (14 CIAs from four classes), aquaculture sector (3 CIAs from 1class)

2017
2019
2020
2021
Big gaps in food-animal and crop sector

- No data on how much and what kind of antibiotics are used in food-animals and crops in public domain
- No law to regulate feed and use of antibiotic growth promoters continue
- Not much recognition of the need to address disease preventative use of antibiotics
- No law on CIAs, other than colistin—many still being used
- National level standard treatment guidelines for veterinary sector not there
- No data on antibiotic residues in food from animals other than milk survey
- No specific guidelines/standards to make animal farm waste AMR safe
CSE assessment of the National Dairy Development Board’s project on *ethnoveterinary medicines* implemented with technical support from Trans-Disciplinary University, Karnataka

*Alternative to antibiotics in Indian dairy sector*
Use of ethnoveterinary medicines in the Indian dairy sector

Preparation at home:
- Aloe vera, turmeric, lime (calcium hydroxide), and mustard oil

Commercial preparation:
- Ethnoveterinary formulations for important ailments in bovines
Use of ethnoveterinary medicines on reducing antibiotic use in the Indian dairy sector

Data analysed between 2016-October 2022

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of unions/producer companies treating with EVM</th>
<th>Total no of cases treated across unions (in thousands)</th>
<th>Cure rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastitis</td>
<td>25</td>
<td>255</td>
<td>78.4</td>
</tr>
<tr>
<td>Fever</td>
<td>18</td>
<td>163</td>
<td>82.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
<td>151</td>
<td>84.4</td>
</tr>
<tr>
<td>Indigestion</td>
<td>19</td>
<td>32</td>
<td>83.4</td>
</tr>
<tr>
<td>Wound</td>
<td>16</td>
<td>9</td>
<td>80.5</td>
</tr>
<tr>
<td>Bloat</td>
<td>18</td>
<td>7</td>
<td>76.0</td>
</tr>
<tr>
<td>Retention of placenta</td>
<td>17</td>
<td>6</td>
<td>71.2</td>
</tr>
<tr>
<td>Lumpy skin disease</td>
<td>8</td>
<td>3</td>
<td>66.2</td>
</tr>
<tr>
<td>Prolapse</td>
<td>17</td>
<td>2</td>
<td>69.6</td>
</tr>
<tr>
<td>Sub-total</td>
<td></td>
<td>628</td>
<td>80.9</td>
</tr>
<tr>
<td>Other ailments</td>
<td>152</td>
<td></td>
<td>78.3</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>780</td>
<td>80.4</td>
</tr>
</tbody>
</table>

- 7.8 lakh disease cases across all 25 unions

- Overall 80.4% cure rate—4 out of every 5 animal were cured with EVM

- Cure rate for mastitis was 78.4%
What do these results mean?

Double benefits of ethnoveterinary medicine

Reduction in veterinary visits 2017-2021 at Sabar Dairy in Gujarat

- Safe milk and milk products for consumer
- Reduction in overall treatment expenses
- Improved livelihood of farmers
Managing environmental AMR spread
Structuring the environmental AMR problem
It is cross-cutting, complex

<table>
<thead>
<tr>
<th>Point Sources</th>
<th>Non-point sources/reservoirs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farms</td>
<td>Rivers, Reservoirs</td>
</tr>
<tr>
<td><strong>Waste from:</strong></td>
<td>Groundwater</td>
</tr>
<tr>
<td>Animal farms: poultry, dairy, pig, fish etc.</td>
<td>Agricultural soil</td>
</tr>
<tr>
<td>Agriculture/horticulture farms</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Factories</td>
<td></td>
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<tr>
<td><strong>Effluents from:</strong></td>
<td></td>
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<tr>
<td>Pharmaceutical manufacturing</td>
<td></td>
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<tr>
<td>Through CETPs catering to pharma industry</td>
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<tr>
<td>Feed mills</td>
<td></td>
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<tr>
<td>Slaughter houses</td>
<td></td>
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<tr>
<td>Processing units (meat, dairy)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Households/Community</td>
<td></td>
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<tr>
<td><strong>Effluents from:</strong></td>
<td></td>
</tr>
<tr>
<td>Sewage treatment plants</td>
<td></td>
</tr>
<tr>
<td>Disposal of unused, expired drugs</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare Settings</td>
<td></td>
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<tr>
<td><strong>Hospital sewage</strong></td>
<td></td>
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<tr>
<td>Waste from veterinary care settings, laboratories etc.</td>
<td></td>
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</tbody>
</table>

Three AMR determinants (antibiotic residues, resistant bacteria, antibiotic resistance genes) travel across multiple sectors; Nature of waste and AMR determinants varies across sectors and local context.
CSE’s work on AMR in environment

- AMR in poultry environment (2017)
- Disposal of unused antibiotics (2019)
- Disposal of pharma manufacturing waste, 2017
- Containing antibiotic pollution from manufacturing (2023)

*Antibiotic pollution from **pharmaceutical waste** is receiving traction in global policy/trade discussions.*
Where do we stand today?
Awareness, capacity and resources – a big challenge

- Environmental AMR containment is part of National Action Plan, but progress on the ground is less than adequate. Reasons include:
  - **Limited know-how, data and capacity** – environmental regulators less aware about microbiological aspects and more experienced in chemicals/analytical chemistry; historical focus - pesticides, heavy metals etc.
  - **Limited technical global guidance** – monitoring, waste management
  - **Over-dependence on surveillance** – resource-intensive; technically demanding
  - **Cost-effective aspects of prevention often overlooked** (such as less use, less waste, less resources to clean up)
  - **No/limited environment AMR related funding** within the overall limited funds for AMR
Implementing National Action Plans effectively
CSE has contributed on the animal and environmental dimensions of AMR to inform National Action Plans of LMICs

Report on containing the silent pandemic of AMR, 2021

Zambia's Multi-Sectoral National Action Plan on Antimicrobial Resistance

Promotion Activities of Zambia's Multi-Sectoral National Action Plan on Antimicrobial Resistance

Baseline Information for Integrated Antimicrobial Resistance Surveillance in Zambia

Zambia's Integrated Antimicrobial Resistance Surveillance Framework

Roadmap to Phase Out Non-Therapeutic Antibiotic Use and Critically Important Antibiotics in Food-Animals in Zambia

CSE engagement in Zambia, 2019-20

2017

2021

April

2024
National developments to contain AMR

CSE was involved in development of India’s National AMR Action Plan and State Action plans of Kerala, Madhya Pradesh and Delhi;
Key government action in India so far: Centre and States

- **FSSAI** standards (since 2018) for residual antibiotics in food from animals
- **MoHFW** ban on use of colistin in food animals (2019)
- **MoA** draft order to phase out/prohibit streptomycin and tetracycline use in agriculture (2021): notified from Feb 2022; complete ban to be enforced from Jan 2024; phase out on condition of availability of alternatives
- **CPCB** guidelines on management of poultry and dairy sector waste (2020 and 2021)
We need solutions; we need to do things differently

• Our solutions have to be **cost effective, technically less demanding** and **relevant to the local context**.

• We need to focus on **prevention**:
  
  – **Prevention at farms** means less disease, less antibiotic use, less clean up required- clean water, alternatives, good animal housing and farming practices
  
  – **Prevention at factories** means better process controls, less waste, low-cost waste management technologies, low-cost monitoring
  
  – **Prevention also means better Water, Sanitation and Hygiene**

• We have to **make animal-farm waste AMR safe** for agriculture use.
  
  – Manure as organic fertilizer is a huge resource, which if efficiently used can save cost, energy, chemical contamination and environmental degradation.
  
  – It supports agro-ecological practices, which are suitable to transform food systems/agriculture to make them sustainable
One Health approach is critical

- That the way we produce our food and the way we manage our waste/environment is connected to our health and the health of planet

- One Health is strongly linked with development, commerce and trade

- But most importantly, ONE HEALTH RESPONSE TO AMR has co-benefits related to limiting zoonoses and pandemics, ecological conservation, livelihood security and climate resilience
Thank you!

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