Antimicrobial Resistance

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Why AMR in ATM training?

- Antibiotic~Antimicrobial
- Similarities and Differences with Climate Change agenda.
- Access, R&D and Regulatory issues (OTC, Standard tt Guidelines).
- Lack of Access jeopardizing Access for those who have it?
- Only drug where usage affects the entire ecosystem.
- Access to diagnostics and Health Systems.
- Industry versus Civil Society (diagnostics, drugs, technical guidelines)
- Health Security in the absence of health? (Snakes on a plane)
Outline

1. Extent of the Problem
2. Causes
3. Analysis & Interventions
4. Causes of the Causes from the health systems
5. Policies & Role of CSOs

Group Discussions

Group 1. Implications of AMR on SDGs.
Group 2. Reflecting on the Progress on Global Action Plans after two years.
Group 3. Tripartite agency roles in AMR Access and Stewardship.
Group 4. AMR and PHC- Are they connected?
Group 5. The critique of Keenan et al mass prophylaxis and implications on AMR
1. Extent of the problem
Deaths attributable to AMR every year compared to other major causes of death

- AMR now 700,000 (low estimate)
- Tetanus 60,000
- Road traffic accidents 1.2 million
- Measles 130,000
- Diarrhoeal disease 1.4 million
- Cancer 8.2 million
- Cholera 100,000 – 120,000
- Diabetes 1.5 million

AMR in 2050
10 million

Deaths attributable to AMR every year by 2050

Extent of the Problem

• 3 agents of greatest concern- *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* (WHO, 2014).

• Gram Negative Organisms

• Massive Public Health Concerns- HIV, TB, Malaria.

• MDRs- TB, Malaria, Typhoid; XDR/TDRs- Malaria, TB

• Resistance to last-resort antibiotics leading to hard to treat epidemics, such as- MRSA, ESBL-producing Enterobacteriaceae, CRE, NDM-1, VRE, and gonorrheal infections.
E Coli

Klebsiella pneumoniae

Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011–2014).

Staphylococcus aureus

Antibiotic driven resistance evolution
Quinolone-MRSA

Source: Johnson and Woodford 2013 (adapted) from The State of the World’s Antibiotics 2015 (CDDEP).
<table>
<thead>
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<th>AMR Burden quantification</th>
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<td>Longer illness, higher mortality</td>
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Economic Burden Projections

• Impact on GDP: By 2050, annual global GDP would fall by 1.1% in the low-impact AMR scenario and 3.8% in the high-impact AMR scenario.

• Impact on global poverty: Of the additional 28.3 million people falling into extreme poverty in 2050 in the high-impact AMR scenario (26.2m from LIC).

• Impact on healthcare costs: Global increases in healthcare costs may range from $300 billion to more than $1 trillion per year by 2050.

Source: World Bank
2. Causes
Antibiotic Resistance – causes and effects

Antibiotics are medicines that attack bacteria in different ways to damage the structures and functions that distinguish bacterial cells from human cells, such as the cell walls of bacteria.

> Multiresistant bacteria
A bacterium that is resistant to several antibiotics is multidrug resistant. The genes coding for different resistance mechanisms can reside on a plasmid, and be transferred together from one bacterium to another.

Example of resistance mechanisms:
A Pump that transfers the antibiotic out of the bacterium
B Enzyme that degrades the antibiotic
C Enzyme that alters the antibiotic thus making it inactive

> Selection of resistant bacteria
Resistance to antibiotics often occurs gradually in a bacterium through random mutations or through transfer of a piece of DNA from another resistant bacterium.

LOW RESISTANCE LEVEL
1 The original population is exposed to antibiotic treatment

HIGH RESISTANCE LEVEL
2 Only the resistant bacteria survive...
3 ... and can multiply unimpeded when competition for food decreases.

Plasmid
ring-shaped DNA molecule, in this case with information on the different mechanisms of resistance (antibiotic resistance genes)

= different forms of antibiotics

Source: European Centre for Disease Control and Prevention
How does antibiotic resistance spread?

Antibiotic resistance is the ability of bacteria to combat the actions of one or more antibiotics. Humans and animals do not become resistant to antibiotic treatments, but bacteria carried by humans and animals can.

1. Animals may be treated with antibiotics and they can therefore carry antibiotic-resistant bacteria. Vegetables may be contaminated with antibiotic-resistant bacteria from animal manure used as fertilizer. Antibiotic-resistant bacteria can spread to humans through food and direct contact with animals.

2. Humans sometimes receive antibiotics prescribed to treat infections. However, bacteria develop resistance to antibiotics as a natural, adaptive reaction. Antibiotic-resistant bacteria can then spread from the treated patient to other persons.

3. Humans may receive antibiotics in hospitals and then carry antibiotic-resistant bacteria. These can spread to other patients or to people whose hands or contaminated objects. Patients who carry these bacteria may spread them directly to other persons.

4. Travellers requiring hospital care while visiting a country with a high prevalence of antibiotic resistance may return with antibiotic-resistant bacteria.

5. Staff in contact with healthcare travellers may carry and impart resistant bacteria acquired from food or the environment during travel.

6. In the community, people may carry resistant bacteria from their local environment.

7. Through travel, people may carry resistant bacteria from their local environment.

8. In healthcare facilities, people may carry resistant bacteria from their local environment.

Source: European Centre for Disease Control and Prevention
ANIMALS IN THE USA CONSUME MORE THAN TWICE AS MANY MEDICALLY IMPORTANT ANTIBIOTICS AS HUMANS

30% consumed by humans

70% are consumed by animals

HOW ANTIMICROBIALS REACH THE ENVIRONMENT

- Manufacture of antimicrobials
- Waste
- Use
- Humans
- Crops
- Animals including livestock, aquaculture and pets
- Water treatment systems

Environment

MOST ANTIBIOTICS USED IN ANIMALS ARE MEDICALLY IMPORTANT FOR HUMANS

Of the 41 antibiotics* that are approved for use in food producing animals by the FDA, 31 are categorised as being medically important for human use.

31 are deemed medically important

10 are not currently deemed medically important

HEALTHCARE-ASSOCIATED INFECTIONS ARE A CONCERN IN ALL COUNTRIES

7 to 10%
Of every 100 hospitalised patients, 7 in high-income and 10 in low and middle-income countries, will acquire at least one healthcare-associated infection.

1 in 3
A third of patients in intensive care units (ICUs) in high-income countries are affected by at least 1 healthcare-associated infection.

1 in 4
A quarter of healthcare-associated infections in long-term acute care settings are caused by antibiotic-resistant bacteria.

POOR INFECTION CONTROL CONTRIBUTES TO INCREASED RESISTANCE AND LOSS OF LIFE

- Increasing incidences of infectious diseases
  - Increase in antimicrobial use
  - Increase in antimicrobial resistance

- More deaths, lower quality of life

- Poor hygiene, infection control and sanitation

3. Analysis & Interventions
LOWERING DEMAND FOR ANTIMICROBIALS AND REDUCING UNNECESSARY USE

- Public awareness
- Sanitation and hygiene
- Antibiotics in agriculture and the environment
- Vaccines and alternatives
- Rapid diagnostics
- Human capital

WASH and IPC

- 494 million cases of diarrhoea are treated with antibiotics each year in Brazil, Indonesia, India and Nigeria alone.

- Universal access to improved water and sanitation in these four countries could cut this number by 60%. (O’Neill’s Review)

- WASH could decrease diarrhoea, typhoid, campylobacter and many other diseases.

- IPC breaks the chain of transmission.
Use in Animals & Agriculture

- Economically not as beneficial as it was previously thought to be.
- Far worse in aquaculture, residues remaining for an extended period of time, and in water.
- Type of farms. Intensive more.
- World food production’s heavy reliance on fungicide is too difficult to eliminate. O’Neill’s report suggest that new classes of clinical antifungals (developed in the future) should be banned from use in food production.
Access to Diagnostics

- Diagnostics in the USA guide 60–70% of health decisions, but accounts for only 2% of health expenditures, LMICs are even lower (Lewin Group reports).

- Caution.

- A clinical algorithm now allows community health workers to make a presumptive diagnosis of acute lower respiratory infection, but had a better diagnostic been available, unnecessary treatments might have been avoided. (Lim, Nature, 2006)

- Distrust in the quality of diagnostics, the paucity of timely results from diagnostic tests, and the fear of poor outcomes, can prompt clinicians to set aside diagnostic test findings. (Anthony So, Lancet 2013).

- Improved diagnosis—part technology, part syndromic management—can reduce uncertainty about whether to treat with antibiotics or not. (Anthony So, Lancet 2013).
Crucial issues intersecting with access to medicines
Crucial issues intersecting with access to medicines

1. Best possible example of the failure of current R&D mechanism, advocating delinkage and increased public funding in R&D.
Is pharma supporting the public health responsibly through their R&D?

In 1990, 18 pharmaceutical corporations had active programs to address antimicrobial resistance. By 2010, only four remained.

Last year.

Source: The Review on Antimicrobial Resistance
No new antibiotic class since 1987. Why?

- 61 new ab FDA approvals during 1990-2009, most (26) withdrawn d/t unclear reasons. (6 d/t safety concerns).

- The withdrawals are the highest among all the classes of drugs put together.

- Market approval & withdrawals- Clinical + commercial success amidst externalities.

- Antimicrobial R&D clearly points towards the failure in current R&D system.

- Granting patent monopolies to pharmaceutical companies as the main way to incentivise innovation has led to this state; where 60% funding for profitable disease R&D is private, whereas for HIV, TB, Malaria and others- >2/3rd funding is public and only 10% private! (UNHLP)

Public funding in R&D needs a boost to decrease dependence
Crucial issues intersecting with access to medicines

1. Best possible example of the failure of current R&D mechanism, advocating delinkage and increased public funding in R&D.

2. The regulation politics, evidence and finger pointing.
Regulations (Prescriptions, guidelines, OTC only)

- **Quick guideline implementations.** Though warnings of resistance to co-trimoxazole in *Streptococcus pneumoniae* came early, it took many years for the recommendations to change (to amoxicillin) and even longer to implement the recommendations. (Okeke et al. Lancet 2005, Feikin et al. J Infectious Dis 2000, Dauilare et al J Law Med Ethics 2015)

- SAM Antibiotics controversy (Amoxycillin)- Malawi study versus Niger-MSF study. Urgent research needed.

- Inequity Lens: Pathologization of ‘self medication’ in poor health systems (Das & Das, 2006).

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Prescription only access to antibiotics could exacerbate health inequalities in LMICs

August 23, 2018

One standardised solution to antimicrobial resistance will not be appropriate across all settings, say Mishal S Khan and colleagues

Cambodia (BMJ blogs)
Crucial issues intersecting with access to medicines

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3. Access and Rationality
Rational Use & Access

“how to ensure that when [patients] need drug therapy the appropriate drug is prescribed for them, it is effective and of acceptable quality and safety, it is available at the right time at a price they can afford, it is dispensed correctly and it is taken in the right dose at the right intervals and for the right length of time”. (WHO 1987)

<table>
<thead>
<tr>
<th>Therapeutic access</th>
<th>refers to the bottlenecks—scientific &amp; financial—in bringing new antibiotics to market.</th>
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<tbody>
<tr>
<td>Structural access</td>
<td>addresses the obstacles to delivering antibiotics effectively in the system and using them rationally at the clinical level in-country.</td>
</tr>
<tr>
<td>Financial access</td>
<td>characterizes the difficulty in affording a rational course of antibiotic treatment.</td>
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</table>
Do qualified practitioners necessarily prescribe more rationally?

- Guideline based systems (NICE) versus mixed systems [Type 1 and Type 2 errors- (Social Policy, EPW)]

- Medical curriculum and source of continuous drug information

Presumptive & Overuse reasons-

1. Pressure to Prescribe,
2. information asymmetry at the user, prescriber, or provider levels
3. diagnostic uncertainty & access
4. the many financial incentives for overprescription (China Hospitals)
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4. **Access, but not Excess**
Access - Excess

Pneumonia

<1/3rd under 5s receive ab (eg amox) in LMICs (UNICEF, 2012)

Inequality

Extremely pronounced gap between richest & poorest quintiles (Johannsen et al, 2012)

Pneumonia+Sepsis

> 1 million children every year die due to such untreated infections. (Lancet 2016).

Diarrhoea & Cold & Cough
Penicillin is the only drug to prevent mother to child syphilis.

An ongoing penicillin shortage is currently affecting at least 39 countries, now including Brazil, Germany, the Netherlands, the US and India.

Neisseria Gonorrhoea is WHO high priority pathogen for R&D of new antibiotics
Every new generation is exponentially more expensive than its predecessors.
<table>
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<tr>
<th>Access</th>
<th>Watch</th>
<th>Reserve</th>
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<tr>
<td>• 1(^{st}/2^{nd}) choice for reviewed indications</td>
<td>• ↑resistance potential • 1(^{st}/2^{nd}) choice for specific indications</td>
<td>• Last resort • For highly specific, when all alternatives have failed.</td>
</tr>
<tr>
<td>• Should be available, affordable &amp; quality assured</td>
<td>• WHO Essential List, 2017’s big change focusing on stewardship.</td>
<td>• Implementional challenge in poor/complex health systems.</td>
</tr>
<tr>
<td></td>
<td>• Medical curriculum</td>
<td>• Penicillin?</td>
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Crucial issues intersecting with access to medicines

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4. **Access but not Excess**

5. Substandard
Substandard

• 7% antibiotics worldwide are falsified/substandard (WHO). Most commonly reported classes of medicines: antimalarials and antibiotics.

• Projection for childhood pneumonia: 72 430 deaths can be attributed to the use of medical products with reduced antibiotic activity. If they have no activity at all, the estimated death toll rises to 169 271.

• Area of concern to counter Industry’s IP and monopoly agenda.

• MIC
Crucial issues intersecting with access to medicines

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4. **Access but not Excess**

5. Substandard

6. **FDC- rationality & irrationality**
FDCs

- 64% of antibiotics (75 of the 118 antibiotic fixed-dose combination (FDC) in India were completely irrational!

- Campaigns by PHM and civil society organizations instrumental in getting the ban.

- TB, HIV, ACT
  - Potential combinations with different mechanisms of action
  - Norfloxacin-Tinidazole
  - Amoxicillin-Cloxacillin etc.
4. Causes of the Causes from the health systems
The resistance is higher in countries with lower consumptions

Why?

Reflecting on Causes of the Causes
Upstream factors driving AMR: forgotten in AMR strategies

- Public Health Expenditure (GDP/capita)
- Regulation of Private sector
- Lower Private health Spending
- Indicative of better sanitation, access to clean water, and access to refrigeration.

- In Europe, Antibiotic Consumption is the driver.
- But, the increase in education/GDP/person increases AMR.
5. Policies & Role of CSOs
In May 2015, the 68th World Health Assembly adopted the Global Action Plan on AMR.

“One Health”

Recognizing that the main impact of antimicrobial resistance is on human health, but that both the contributing factors and the consequences, including economic and others, go beyond health, and that there is a need for a coherent, comprehensive and integrated approach at global, regional and national levels, in a “One Health” approach and beyond, involving different actors and sectors such as human and veterinary medicine, agriculture, finance, environment and consumers.

Policies

• A landmark development at global level is the adoption on 21 September 2016 of a **Political Declaration on AMR** by the heads of states and governments at a high level event on AMR. It was subsequently formally adopted by the General Assembly.

• the Declaration recognised the importance of **delinking the cost of investment in R&D** from the price and volume of sales so as to facilitate equitable and affordable access to new medicines, diagnostic tools and vaccines.

• In 2017, the **Interagency Coordination Group (IACG)** was established by the UNSG to follow up on the Declaration, with 6 subgroups.

• The report of the IACG will be submitted to the UNSG who will present his own report to the UN General Assembly in 2019.
Declaration on Antibiotic Resistance

Antibiotic Resistance Coalition

Original signatories: Alliance to Save Our Antibiotics • Centre for Science and Environment • Center for Science in the Public Interest • Consumers International • Duke University's Program on Global Health and Technology Access • Food Animal Concerns Trust • IFARMA Foundation • Initiative for Health & Equity in Society • Institute for Agriculture and Trade Policy • Health Action International • Health Care Without Harm • Healthy Food Action • Keep Antibiotics Working • Peoples Health Movement • Public Citizen • ReAct – Action on Antibiotic Resistance • South Centre • Sustainable Food Trust • Third World Network • Universities Allied for Essential Medicines • What Next Forum • 22 May 2014 • For signing onto the declaration contact signon@arcedclaration.org •
Role of CSOs

• The AMR agenda has been co-opted by the pharmaceutical industry in the name of selling non-essential antibiotics and squandering new money on drug development.

• AMR-Industry Alliance.

• Not enough CS Activism

• Unbalanced innovation: Drug development agenda has undermined investments in other areas of innovation – including health systems delivery, food production or development of other medical tools for humans and animals (diagnostics and vaccines).
An example of AMR Watch in action
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• Group 4. AMR and PHC- How are they connected?

• Group 5. The critique of Keenan et al mass prophylaxis and implications on AMR
2. Global Action Plan on AMR

5 strategic objectives are:

- **Objective 1:** Improve **awareness and understanding** of antimicrobial resistance through effective communication, education and training.
- **Objective 2:** Strengthen the knowledge and evidence base through **surveillance and research**.
- **Objective 3:** Reduce the incidence of infection through effective **sanitation, hygiene and infection prevention measures**.
- **Objective 4:** **Optimize** the use of antimicrobial medicines in human and animal health.
- **Objective 5:** Develop the **economic case** for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.
5. Rational versus Irrational prophylaxis

- Keenan et al 2018 → Mass Azithromycin use to decrease child mortality!
- Landlier et al., 2018 → targeted mass antimalarial administration reduced malaria incidence in hotspot areas
- Schwartz et al., 2015 → BMI gain and obesity predisposition were associated with a history of antibiotic use in children
- Trehan et al, 2013- Routine Antibiotics to ‘uncomplicated SAM’ with RUTF on an outpatient basis.
- Rea et al. 2016 → Antibiotic disruptions to microbiota in early life (a period of dynamic microbiota-host interactions) can alter gut-brain signalling, affect lifelong health and increase the risk of neurodevelopmental disorders.
Thank You
Hope from the antibiotic pipeline

By 2023, GARDP aims to register a new drug for gonorrhoea in a number of high burden Countries. Zoliflodacin is in phase III.

The antibiotic pipeline

As of December 2014, at least 37 new antibiotics, developed by 32 mainly small companies, were in the development pipeline for approval in the United States. Eight of these were in Phase 3 (the final stage, involving large-scale clinical trials), and for one, a new drug application had been submitted to FDA for approval (Pew Charitable Trusts 2014). At least two of the drugs in the early phase of development use novel mechanisms to attack bacteria by circumventing bacterial resistance to available antibiotics. Of the drugs, 22 are potentially effective against Gram-negative pathogens (Table 4-3).

In 2015, teixobactin, an antibiotic belonging to a new class, was discovered through the novel growth of uncultured organisms in a laboratory at Northeastern University. Preliminary tests did not reveal any resistance to the compound by *Staphylococcus aureus* or *Mycobacterium tuberculosis*. Teixobactin may prove to be the first antibiotic with the potential to avoid or delay the development of resistance (Ling et al. 2015).

The deficit of greatest concern is a lack of new drugs in the pipeline to treat Gram-negative infections, particularly...