OASIS One Health Antibiotic Stewardship in Society

How can antibiotic use be optimised in Indian community settings?

Antimicrobial resistance (AMR) is a major global health threat. It is increasing day by day due to the inappropriate use and management of antibiotics in human, animal and environmental health, by many different actors. These include communities, healthcare providers, industry stakeholders and the health and regulatory systems. Urgent multi-stakeholder action is needed to optimise antibiotic use across different sectors and different actors. This brief highlights the patterns and drivers of antibiotic use in human and animal health in the community setting in eastern India, with broader implications for rural India . It includes recommendations for optimising antibiotic use in the community setting.

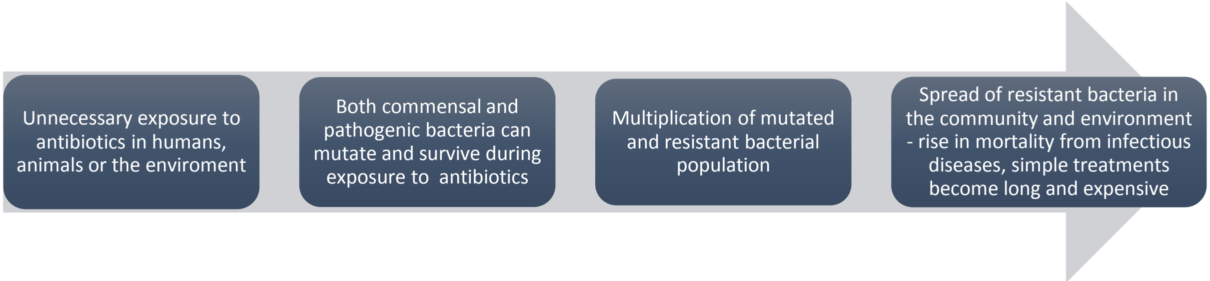
Key messages

- India is the world's largest consumer of antibiotics for human health and the fourth largest for animal husbandry and animal health. It has among the highest levels of AMR in the world along with a high burden of infectious disease.
- Informally trained private providers (IPs) and Para veterinarians (paravets) are a key source of primary healthcare and antibiotics, for people and for animals, in rural India. However, they are neglected in AMR policies and action plans.
- A majority of healthcare providers, both informal and formal, paravets as well as veterinarians, dispense and prescribe antibiotics excessively and in non-standardised ways.
- There are multiple drivers of non-standardised antibiotic use by informal providers and paravets: lack of knowledge and proper guidelines, clinical mentorship by doctors and vets who also prescribe inappropriately, lack of appropriate veterinary formulations and drug outlets, community expectations and affordability, economic incentives from drug sales, and pharmaceutical drug promotion and incentivization.
- The mutual interdependencies amongst all these actors have shaped an alternative healthcare delivery system and an antibiotic supply chain, that supplements the public health system in rural areas.
- Regulations are difficult to enforce in this scenario out of fears that doing so would adversely impact people's immediate access to healthcare and medicines.
- However current regulations restrict antibiotic sales to qualified prescribers and therefore present a barrier for practical solutions that will require some antibiotics to be accessible through lesser qualified and trained providers.
- Efforts to optimise antibiotic use in these settings must ensure that people's access to essential antibiotics is maintained while excessive and inappropriate use is reduced. These efforts will need to target multiple stakeholders involved in these settings.

What is antimicrobial resistance?

AMR is the ability of bacteria, viruses and fungi to protect themselves against the actions of antimicrobials, **especially antibiotics**, which are the world's most powerful weapon against life threatening infectious diseases (Fig. 1). Increasing rates of AMR could lead to a frightening scenario where treating the commonest diseases such as pneumonia, dysentery and urinary tract infections will become complicated, prolonged and costly[1]. Other alarming consequences of AMR are the emergence and rapid global spread of 'superbugs': bacteria that are resistant to multiple antibiotics, such as methicillin-resistant *Staphylococcus aureus (MRSA) and* extensively drug resistant tuberculosis (XDR TB), resistant to both first- and second-line treatments [2]. An estimated 700,000 people die annually due to drug-resistant infections; if current trends continue, this could increase to 10 million deaths every year by 2050[3]. However, in many low- and middle-income countries, many people still lack access to essential antibiotics, a scenario that leads to an estimated 5 million deaths annually[4].

Fig.1: How do bacteria become resistant?



What is antibiotic stewardship?

Antibiotic stewardship is a strategy to ensure that antibiotic use is optimised, i.e., the right antibiotic is given to the right patient at the right time and in the right dosage. This means reducing excessive and inappropriate use of antibiotics, while ensuring access to essential antibiotics for all those who need them.

An overview of AMR in India

India is the world's largest consumer of antibiotics (6.3 billion DDDs) followed by China (3.8 billion DDDs) and the United States (2.9 billion DDDs)[5]. More than 70% of antibiotics consumed in India are from WHO's WATCH group of antibiotics (WHO), and less than 30% are from the ACCESS group. WHO recommends that WATCH antibiotics should be sparsely used and monitored carefully due to their higher resistance potential[6]. ACCESS antibiotics should be widely available as first line treatments and should comprise 60% of a country's antibiotic consumption. This is not happening in India. Moreover, the consumption of RESERVE antibiotics like carbapenems, that are last resort antibiotics used to treat infections caused by multidrug resistant (MDR) pathogens, also increased in India between 2000 and 2015[7].

India is among the nations with the highest burden of bacterial infections. An estimated 410,000 children aged five years or less die from pneumonia in India annually; with pneumonia accounting for almost 25% of all child deaths. The crude mortality from infectious diseases in India today is 417 per 100,000 persons. Consequently, the impact of AMR is likely to be higher in the Indian setting.

National Action Plan for AMR 2017-21, Government of India

India has the highest Drug Resistance Index (DRI) among several LMICs[8] (see Fig. 2) Surveillance data show that 50% of *K.pneumoniae* and 60% *of E.coli* isolates are resistant to ciprofloxacin and more than 80% are resistant to cefotaxime and ceftriaxone[9]. All these are WATCH group antibiotics and among the first line treatments for conditions like bacterial diarrhoea and typhoid fever.

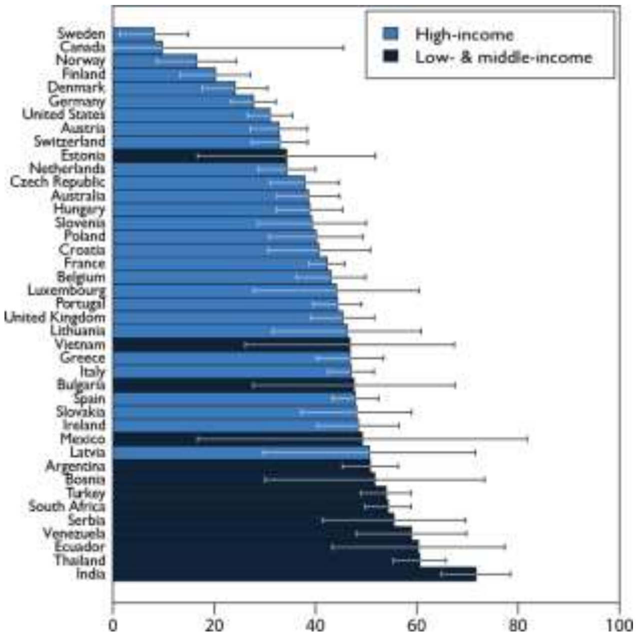


Fig.2: Drug Resistance Index across Countries
Each bar represents the drug resistance index (DRI) for countries reporting resistance for five or more pathogens and 15 or more pathogen-antibiotic combinations for at least one year between 2012 and 2015 [8]

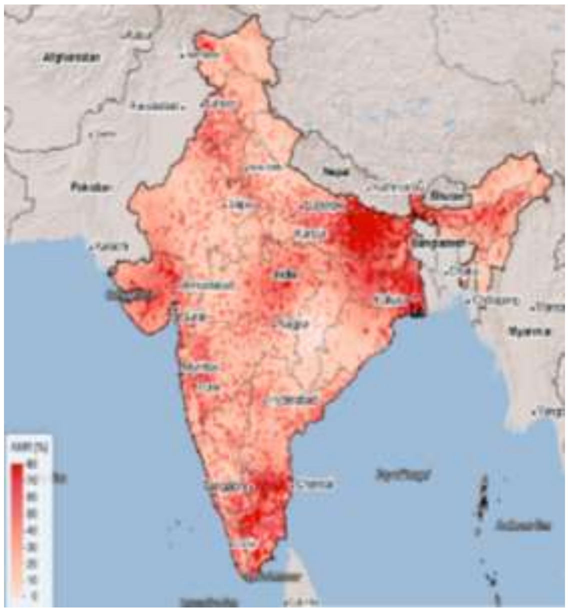


Fig.3: Prevalence of antibiotic resistance bacteria in diverse livestock in India [12].
West Bengal, Bihar, Tamil Nadu were identified as hotspots for prevalence of antibiotic resistant bacteria in livestock

The One Health Antibiotic Stewardship in Society Study (OASIS)

The OASIS study (Aug. 2016- Jan 2022)was designed to understand antibiotic use and its drivers in human and animal health in India. Study findings will inform the co-design of an antibiotic stewardship intervention.

Study objectives were to:

1. Understand the patterns and drivers of antibiotic use by informal providers of human health
2. Understand the patterns and drivers of antibiotic use in backyard livestock production and its overlaps with human health
3. Map formal and informal supply and value chains related to human and animal antibiotics in the local context to provide an overall understanding of flows of antibiotics to different providers
4. Identify existing channels and platforms for community awareness building and influencing behaviour change.
5. Use the study findings to co-design an antibiotic stewardship intervention focusing on IPs and paravets and assess its feasibility and acceptability, and barriers and enablers.

Study sites were located in districts South 24 Parganas and Birbhum in West Bengal.

Study methods were a mix of quantitative and qualitative techniques. We **surveyed 300 IPs** in randomly selected village clusters and conducted **in-depth interviews** with 30 IPs, 38 livestock owning households, 20 animal healthcare providers, 40 stakeholders (pharmaceutical, medical and health and regulatory officials), 14 community health workers and 14 community leaders. Twenty-six group discussions were conducted with community members. We interviewed stakeholders who occupy various roles within the antibiotic supply chain to better understand and map the supply chain from the manufacturer to the end consumer, including its particularities. This was complemented by the perspectives of communities and stakeholders in the formal health and regulatory system, and in the pharmaceutical industry to inform a comprehensive analysis of the factors influencing the supply of antibiotics to human patients by informal providers, and to backyard animals by paravets.

Study Findings

1. Informal providers' and paravets' central role in antibiotic provision

Who are informal providers (IPs) and paravets?

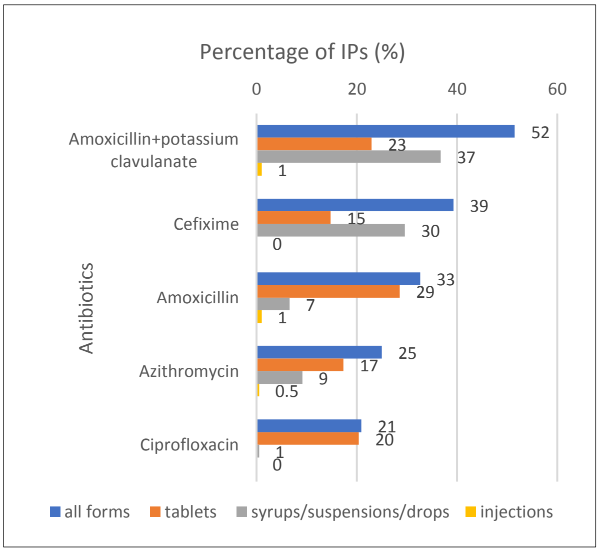
IPs are private healthcare practitioners found all over rural India and in less affluent urban areas. They account for more than 70% of healthcare visits in rural India [10] but are not medically qualified. In our study, all IPs had completed high school and 1/3rd were graduates or postgraduates. 7% had a pharmacy diploma, 1% had a lab assistant's certificate, and around 70% had a paramedical or primary care certification. They practiced out of small clinics, typically open 7 days a week. All dispensed and/or prescribed antibiotics [11].

Paravets include public and private para veterinary professionals. In our study, *Prani Bandhus* were a public sector cadre trained in artificial insemination and *Prani Mitras* trained in vaccination. They also treated livestock in their private capacity, using antibiotics. This was reported more by *Prani Bandhus* than *Prani Mitras.* There were also private paravets trained by an NGO to increase healthcare access for livestock in remote areas.

Antibiotic provision by IPs

- On average, IPs gave an antibiotic to 50% of their patients daily.
- Amoxicillin (including amoxicillin potassium clavulanate) was the most stocked antibiotic, available in >50 of clinics (Fig.4). More than 50% IPs also reported amoxicillin as the most commonly dispensed antibiotic
- By WHO's classification, 83% IPs stocked a WATCH antibiotic and 71% stocked an ACCESS antibiotic. No RESERVE antibiotics were stocked.
- Antibiotic provision was non-standardised and included sub-optimal dosages and experimentation by switching between antibiotics and changing dosages.

Fig. 4. Top 5 antibiotics stocked by IPs



Antibiotic provision by paravets

- Out of 17 antibiotics used to treat animal diseases, 12 were either critically important or highest priority critically important for human health (see Fig 5)
- Mostly used as first line treatments for various diseases (Fig 5)
- Predominantly for therapeutic use
- In small-scale poultry farms antibiotics were also used prophylactically

Fig. 5. Human antibiotic formulations used in livestock

ANTIBIOTIC	Critically Important Antimicrobial	Highest Priority Critically Important Antimicrobial	Livestock Species	Livestock Disease
AMOXYCILLIN CLAVULANATE	Yes		Cattle	Mastitis
AZITHROMYCIN	Yes	Yes	Poultry, dogs	-
CHLORAMPHENICOL (TOPICAL AND ORAL)			Poultry	Fowl pox, diarrhoea
CIPROFLOXACIN	Yes	Yes	Poultry	"Ranikhet"/ Newcastle Disease
GENTAMICIN	Yes		Cattle,dogs, poultry	Diarrhea etc
HOSTACYCLINE		-	Poultry	Ranikhet
METRONIDAZOLE		-	Cattle, Goats, Poultry	Diarrhoea
NORFLOXACIN	Yes	Yes	Goats	Diarrhoea
OFLOXACIN-ORNIDAZOLE	Yes	Yes	Goats, Poultry, Cattle	Diarrhoea, fever

2. Key Drivers of antibiotic provision by IPs and paravets

2.1. Intrinsic drivers: Limited knowledge ; antibiotics beat competition and protect against income loss

Believing that antibiotics could cure most illnesses, IPs and paravets considered them indispensable for primary care. Only 30% of IPs knew that antibiotics cannot cure viral infections and only 35% associated resistance with bacteria rather than the human body. IPs and paravets feared that without antibiotics patients would not be cured and would not visit them again:

'With regard to treatment, antibiotics are used more than it was before. Antibiotics should be used as less as possible. But we have to use it still, because of the competition. If we can cure the patient fast, then they would call me. If it takes such a long time, they would want to seek other doctors' - a paravet

2.2. Influence of formal prescribers' non-standardised antibiotic use

IPs and paravets were trained and mentored by professionally qualified doctors and veterinarians, who also prescribed antibiotics in non-standardised ways. IPs had close relationships with doctors whom they considered their '*gurus*' and who advised them about treatment, in exchange for patient referrals.

'The doctor Sir told me to give small amount of Monocef [3rd generation cephalosporin] injection on the layer of his skin to check whether the patient has any allergy or not. If it is found okay, then apply the full dosage.' – an IP

Veterinarians also used human antibiotics in animals, and recommended prophylactic use of antibiotics in chicken. Inappropriate use of antibiotics by qualified professionals was attributed to lack of accessible guidelines and local diagnostic capacity, and a competitive market environment incentivized by pharmaceutical companies. Use of human antibiotics in animals was due to inaccessible veterinary drug shops and dispensaries; large pack sizes of veterinary antibiotics that made them too costly for small animals, and a perceived efficacy of human antibiotics in small animals. In the absence of standardised guidelines and lack of a strong counter narrative for antibiotics, most healthcare providers tended to put aside concerns about the long-term impact of resistance over managing short term risks in patients.

2.3. Aggressive marketing and incentivization of antibiotics by pharmaceutical companies

IPs presented a large and growing rural market for pharmaceutical companies who therefore adopted a variety of strategies to promote and sell their products to IPs and paravets. These included conferences (called 'continuing medical education' programmes), free samples and other economic incentives.

'One MR is working from Kolkata to Kakdip (distance of 88kms). His monthly target is rupees 100,000. Rupees 80,000 comes from [selling antibiotics to] the RMPs [local term for informal providers] only. Rest of the rupees 20,000 is earned from the formal doctors.' - a pharmaceutical manager

A pharmaceutical representative lecturing paravets about new drugs

2.4. Regulatory capacity, ethical dilemmas and regulatory barriers

The regulatory departments lacked necessary resources, especially human resources required for monitoring providers, pharmacies and drug outlets. Moreover, regulators were faced with ethical dilemmas about the adverse impact of enforcing regulations on healthcare access. At the same time, it was difficult for health officials to go against the prescription-only regulations for antibiotics and train non-medical providers in the use of a few essential antibiotics to be able to restrict others. The main resistance came from the medical establishment:

'The main problem is MCI [Medical Council of India]. They are not allowing any short course for the informal providers.... the fact is that everyone is concerned about their own boundaries and interests.' (a senior official)

2.5. Community knowledge and expectations

People typically did not demand antibiotics; they needed to recover quickly and at the lowest cost. This resulted in providers giving sub-optimal courses and patients not complying with full courses. Self-medication with arbitrary dosing was common. Local community leaders, health workers and pharmacy shops were important sources of knowledge, but least knowledgeable. Doctors had no time to explain.

3. Recommendations

A complex and diverse web of drivers shape antibiotic access and use by the community-based health workers for human and animal health. These exist at the community, health provider, health and regulatory systems, and pharmaceutical industry levels and include a diversity of actors and their mutual interdependencies. Any antibiotic stewardship interventions targeting the community setting will need to incorporate the positions, vested interests, capacities, and priorities of these multiple stakeholders. Additionally, a meaningful antibiotic stewardship strategy will need to have economic, social, and behavioural components to holistically address all the drivers of inappropriate antibiotic use. These could include, for example, multi-level antibiotic use guidelines and decision support systems for all providers, improved mentorship by formal providers, a code of good antibiotic stewardship practices for the pharmaceutical industry, community awareness programmes and a policy review and dialogue.

Our next step in the OASIS study is to convene a series of stakeholder discussion forums to discuss our findings and co-design potential interventions. If you are interested, please get in touch with us at:

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References:

1.WHO. Global Action Plan on Antimicrobial Resistance. World Health Organization: Geneva, Switzerland, 2015.
2.Seung KJ, Keshavjee S, Rich ML. Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis. *Cold Spring Harb Perspect Med* 2015; **5**(9): a017863-a.
3.O'Neill J. The Review On Antimicrobial Resistance: Tackling Drug-Resistant Infections Globally. UK Government, 2016.
4.Laxminarayan R, Matsoso P, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016; **387: 168–75**.
5.Klein EY, Milkowska-Shibata M, Tseng KK, et al. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: an analysis of pharmaceutical sales data. *The Lancet Infectious Diseases* 2021; **21**(1): 107-15.
6.WHO. The 2019 WHO AWaRe classification of antibiotics. Geneva: World Health Organization; 2019. (https://www.who.int/medicines/news/2019/WHO_releases2019AWaRe_classification_antibiotics/en/.
7.Gandra S, Joshi J, Trett A, Lamkang A, Laxminarayan R. Scoping Report on Antimicrobial Resistance in India. 2017; **Washington, DC: Center for Disease Dynamics, Economics & Policy**.
8.Klein E, Tseng K, Pant S, Laxminarayan R. Tracking global trends in the effectiveness of antibiotic therapy using the Drug Resistance Index. *BMJ Glob Health* 2019; **4:e001315. doi:10.1136/ bmjgh-2018-001315**.
9.WHO. GLASS Country and area profiles, 2018. 2020; **https://apps.who.int/gho/tableau-public/tpc-frame.jsp?id=2012**.
10.Das J, Mohpal A. Socioeconomic Status And Quality Of Care In Rural India: New Evidence From Provider And Household Surveys. *Health Affairs* 2016; **35**(10): 1764-73.
11.Gautham M, Spicer N, Chatterjee S, et al. What are the challenges for antibiotic stewardship at the community level? An analysis of the drivers of antibiotic provision by informal healthcare providers in rural India. *Social Science & Medicine* 2021; **275**: 113813.
12. Van Boeckel TP, Pires J, Silvester R, et al. (2019) Global trends in antimicrobial resistance in animals in low- and middle-income countries. *Science* 365: eaaw19