

# Rethinking the AMR Agenda

World Antimicrobial Awareness  
Week 2021

Compilation of Articles Contributed  
by Experts

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## Why India needs to re-examine its pediatric practices

*Children often receive multiple courses of antibiotics every year since viral infections are recurrent. This makes them more vulnerable to antimicrobial resistance*

By Dhanya Dharampalan  
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Children often receive multiple courses of antibiotics every year since viral infections are recurrent. This makes them more vulnerable to antimicrobial resistance.

India has one of the largest pediatric populations in the world: Those under 18 years comprise over 40 per cent of the country's 1.3 billion.



Pediatric healthcare, therefore, has a critical role in the overall health benefits for the country. It is unfortunate that multi-drug resistant bacterial infections are rampant in this population, which has led to life-threatening serious infections even in a newborn.

The term antimicrobial is used for medicines targeting living microbes. It includes antibiotics for bacterial infections, anti-virals for viral infections, antifungals for fungal infections, and anti-parasitics for infections caused by parasites.

The term broadly defines how medicines that worked efficiently earlier are unable to destroy microbes causing the disease.

An unprecedented rise in antimicrobial resistance globally threatens to reverse the achievements of modern medicine. The biggest driver of antimicrobial resistance is the use of antimicrobials themselves, which leads to selective pressure among the microbes to survive the effect of the antimicrobials and become resistant to their effect.

The resistant mechanisms are passed from one bacteria to another.

The options to treat antimicrobial-resistant bacteria are limited. The drugs are expensive and have side effects. The only solution in hand is to reduce the resistance rates by avoiding antibiotics when not indicated as well as choosing the right drug, dose, interval, route and duration only when needed.

The pediatric population is vulnerable to respiratory and diarrhea infections owing to a weaker immunity compared to the older population. A majority of these infections are caused by viruses that cause fever, running nose, cough and watery diarrhea.

Viral infections are usually self-limiting and require only medicines to relieve symptoms; paracetamol, for example, brings down the fever. A saline nose drop relieves a blocked nose.

Antibiotics that are meant to treat bacterial infections have no effect on viruses. And yet, antibiotics are widely misused.

Children often receive multiple courses of antibiotics every year since viral infections are recurrent. This problem is further precipitated in children who have hypersensitive airways that make them cough whenever there is a change in climatic conditions or pollution levels. These conditions are often mistaken as bacterial pneumonia and are treated unnecessarily with antibiotics.

The problems are multifold. At the prescriber's end, the antibiotic abuse takes place because of difficulty to differentiate between viral and bacterial infections; the latter having an adverse impact if antibiotics are not started in time.

The lack of inexpensive confirmatory tests that can help differentiate between viral and bacterial respiratory infections compounds the challenge. Antibiotics are misused either due to lack of clinical skill / lack of diagnostic facility or the fear and insecurity of losing a patient to another prescriber.

Heavy patient load also causes interference in the time that needs to be devoted for history and physical examination; antibiotics are prescribed more often to safeguard oneself just in case a bacterial infection is missed. Most of these issues can be tackled by training doctors and communicating with parents / guardians on managing symptoms.

For example, parents need to explain that oral rehydration therapy helps a child with watery diarrhea rather than antibiotics.

The antibiotics are many a time misused by users, parents, and patients: They self-medicate by buying antibiotics without a prescription.

We conducted a survey among 800 parents and found that only 28 per cent knew what an antibiotic meant and 15 per cent knew about antibiotic resistance. Many confuse antibiotics for anti-pyretic. They fear that the child's fever will not come down unless an antibiotic is prescribed.

A national guideline released in 2016 included recommended treatment for common illnesses in children. Many antibiotics have been brought under H1 category and with a redline on the label so that these are not sold over the counter without a valid prescription.

The Indian Academy of Pediatrics (IAP) has been actively involved in increasing awareness about antibiotic misuse and practice rational antibiotics. This is being done through educational tools like conferences, webinars, workshops, textbooks, etc.

Yet, there is no system in place to monitor or regulate antibiotic use in the community. The antimicrobial stewardship practices followed by the developed countries rely on leadership commitment, inputs from infectious disease physicians / clinical pharmacists and require resources of time, personnel and IT support.

Extrapolating the same is not possible in a country like ours where resources are limited. Also, such models are suitable only for tertiary centers and not for primary healthcare centers and private clinics.

The 'One Health' approach of addressing all stakeholders is the best way forward. Public awareness about the need for judicious use of antimicrobials needs to be ramped up. This would help physicians to not resort to antimicrobials just for satisfying the health seeker.

We also need better and rapid diagnostic facilities: The availability of rapid diagnostic tests such as rapid malarial antigen test, Dengue NS1 Antigen test, etc has revolutionised the time taken to confirm a clinical diagnosis and give appropriate treatment.

The country needs stringent regulations to avoid irrational antibiotic combinations as well as over-the-counter availability of antibiotics. Vaccination plays an important role in preventing bacterial diseases such as pneumonia, typhoid, diphtheria, meningitis, whooping cough, etc.

A bigger challenge lies in checking irrational use of antimicrobials for common viral illnesses that a majority of children suffer from.

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## The fight to make Kerala antibiotic literate is on

*Kerala was on track to achieve the short-term and long-term targets envisaged under the KARSAP plan to make Kerala antibiotic literate. With COVID-19 having reduced for now, the process can speed up*

By Aravind Reghukumar  
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The Kerala Antimicrobial Resistance Strategic Action Plan (KARSAP) was launched October 25, 2018 by Kerala Chief Minister Pinarayi Vijayan. The introduction of this initiative in the presence of the state health minister, the World Health Organization (WHO) Representative and senior officials from Departments of Agriculture Development & Farmers' Welfare, Animal Husbandry, Environment, Health and Fisheries emphasises that KARSAP is truly a 'One Health' initiative.



KARSAP was the first such state-level action plan to be released in India. KARSAP has six strategic priorities which are aligned with the National Action Plan on AMR as well as the global action plan.

The six strategic priorities reflect the 'One Health' approach and need for inter-sectoral co-ordination. They are:

- **Awareness and understanding:** This includes education, training, communication and IEC activities with regard to AMR in all sectors including human health, animal husbandry, fisheries, dairy, aquaculture, horticulture and environment.
- **Knowledge and evidence:** This includes AMR surveillance and strengthening of laboratory networks in all relevant sectors.
- **Infection prevention and control:** Activities in human health, animal husbandry, environment and community.
- **Optimising use of antimicrobials:** Through regulations and antimicrobial stewardship in humans, animals and food.
- **Innovations, research and development in all relevant sectors.**

Multiple workshops and brainstorming sessions were conducted in 2018 and 2019 involving relevant stakeholders and an action plan was created to achieve the short-term as well as long-term targets identified under KARSAP.

This plan included a roadmap framed with the help of Delhi-based non-profit Centre for Science and Environment for Kerala to phase-out non-therapeutic antibiotic use and to reduce the use of critically important antibiotics (for humans) in the poultry sector.

A framework for AMR surveillance in environment was also drawn up. Recommendations with regard to setting standards for antibiotic residues for effluents from all point sources, upgradation of effluent treatment plans and regulation to ban use of poultry litter in aquaculture were also drafted.

KARS-NET (Kerala antimicrobial resistance surveillance network) was established in 2017 with the help of the WHO country office for India and National Centre for Disease Control (NCDC).

It was established to strengthen laboratory capacity for AMR surveillance in the state and to collate data to generate representative antibiograms for providing evidence based information for action

Initially, the AMR surveillance network included only tertiary care institutions in the government sector. To get representative data from private hospitals, primary and secondary care institutions, KARSAP was systematically expanded to include other institutions, including private medical colleges and laboratories. By end of 2019, KARS-NET had expanded to include 22 satellite centres with GMC Thiruvananthapuram as the focal point.

**KARS-NET objectives are**

- Foster standardisation, strengthening and expansion of AMR surveillance in Kerala;
- Analyse and report KARS-NET data to the state government and NCDC on regular basis;
- Contribute towards the estimation of extent, burden and monitoring of AMR in Kerala; and
- Detect emerging resistance and its spread in Kerala

During the November 2019 annual review of KARSAP activities by the state health minister, it was decided to make Kerala an antibiotic literate / aware state by 2021. World Antibiotic Awareness Week activities carried out in Kerala in November 2019 were focussed on the same theme.

The broad objectives envisaged under the antibiotic literate Kerala campaign are:

- Universal awareness about the importance of having access to antibiotic free food and water.
- Universal awareness about the importance of consuming antibiotics only on doctor's prescription.
- Universal awareness about importance of safely disposing unused or date expired antibiotics. (For this, Kerala has started a unique campaign termed PROUD or Programme on removal of unused drugs, which is a joint venture of the Kerala State Drugs Control Department and All Kerala Chemists and Druggists Association).
- Awareness among school students of the threat posed by AMR.

Till the end of January 2020, all programmes were being conducted as planned and Kerala was slowly but surely on its way to become a truly antibiotic literate state by 2021.

The state was on track to achieve the short-term and long-term targets envisaged under KARSAP within the stipulated time frames. However the emergence of the novel coronavirus disease (COVID-19) pandemic put brakes on the smooth running of KARSAP.

The first case of COVID-19 in India was diagnosed in Kerala January 30, 2020. From then on, the state has prioritised the utilisation of all healthcare resources to tackle the scourge of COVID-19.

This is considering the epidemiological vulnerability of Kerala owing to its density of population which is twice the national average, the large proportion of the elderly due to increased life expectancy and due to increased prevalence of diabetes mellitus and hypertension among the young.

When the state geared up to smother the impact of the 'visible pandemic of COVID-19', it was only natural that activities under KARSAP aimed at 'invisible pandemic of AMR' got disrupted.

#### **Impact of COVID-19 on KARSAP**

- All microbiology labs under KARS-NET started functioning round-the-clock to perform molecular diagnosis of SARS-CoV-2 and hence, antimicrobial surveillance in the state took a back seat. Further expansion of KARS-NET was not attempted due to possible attrition in the wake of COVID-19.
- The link nurses posted in ICUs to capture and audit healthcare associated infections (HCAI), were posted in COVID-19 areas by turn. This loss of continuity impacted capturing HCAI rates like VAP, CA-UTI, CLABSI, SSI etc.
- Antibiotic utilisation metrics calculation was also affected similarly.
- Since the focus was on COVID-19, activities planned to make Kerala antibiotic literate by 2021 could not be carried out. It was decided in the 2021 review meeting to extend the timeline to 2023.
- The annual intersectoral review meeting of KARSAP in 2020 was not conducted.
- Activities planned under environmental surveillance could not be performed in view of the lockdown and other restrictions.
- Since the focus was on COVID-19, research activities under KARSAP also got deferred.

#### **Impact of KARSAP on COVID-19**

- Since all the healthcare workers [HCWs] in the state had already been trained in IPC practices like donning, doffing, droplet and airborne precautions, etc as part of KARSAP, the mortality among HCWs in Kerala is 0.06, which is one of the lowest in the world.
- Adherence to mask etiquette, cough etiquette, social distancing, hand hygiene, etc were high in Kerala, resulting in plateauing of both the first and second COVID-19 waves. This ensured that the number of COVID-19 cases in the state even during the peak of the second wave never exceeded the capacity of healthcare infrastructure. The spreading out of cases over a long period of time in contrast to the rapid peak and descent of the epidemic curve witnessed in other states ensured that Kerala was never short of oxygen or COVID-specific medications. All these contributed to the low COVID-19 case fatality rate in Kerala.
- Adherence to very good IPC practices in ICUs and glycaemic optimisation ensured that incidence of COVID-19 associated mucormycosis in Kerala was very low compared to other states.
- Due to strict adherence to mask and cough etiquette, hand hygiene, etc there was a significant decrease in respiratory infections in the state other than COVID-19. The sale of antibiotics in the state in 2020 was 30 per cent less compared to that in 2019.
- The 'Hub and spoke' model for antimicrobial stewardship pioneered by General Hospital Ernakulam was converted to a hub and spoke model for molecular diagnosis of COVID-19.

To borrow Franklin D Roosevelt's words, 'smooth seas never made skilful sailors', COVID-19 was a tempest that KARSAP had to negotiate. Hopefully the worst is past and we, battered and bruised by the COVID-19 experience, but much wiser, have regrouped and are determined to achieve the seemingly ambitious target of making Kerala an antibiotic literate state by 2023.

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## Surgical site infections worsening globally

*Surgical site infections are the third-most common hospital-acquired infections in the world*

By Bhupinder Singh Kalra and Anurag Mishra  
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Surgical site infections are the third-most common hospital-acquired infections in the world. Photo: iStock

More than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die because of complications caused by resistance to antibiotics, according to 2019 data by the Centers for Disease Control (CDC).

Antimicrobial Resistance (AMR) occurs when infecting microorganisms become non-responsive to antimicrobials, as the microbes develop some intrinsic inheritable changes over time.

Infection, therefore, becomes difficult to treat. This leads to risk of disease spread, severe illness and in some cases, death.

Irrational use of antibiotics is one of the important factors contributing to genesis of multidrug resistant bacteria or microorganisms.

An alarming global spread of 'superbugs' such as *Carbapenem-resistant Enterobacteriaceae* (CRE), Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *Pseudomonas aeruginosa*, etc has become a cause of concern.

Patients who develop infections caused by resistant micro-pathogens are at an increased risk of mortality, morbidity and longer hospital stays.

### **AMR in surgical settings**

The development of antibiotic resistance mechanisms by these bacterial strains has put forward multiple challenges to manage surgical site infections (SSI) globally.

SSIs are the third-most common hospital-acquired infections, accounting for 38 per cent of all nosocomial infections, according to the National Nosocomial Infection Surveillance System of the CDC.

They are associated with prolonged hospitalisation and increased antibiotic therapy costs along with risk of mortality. The most frequently involved microorganisms include *Staphylococcus aureus*, *gram-negative Bacilli*, *coagulase-negative staphylococci*, *Enterococcus* spp. and *Escherichia coli* (*E. coli*).

Methicillin-resistant *S. aureus* (MRSA) represents half of hospital-acquired infections in the United States and Europe.

Colistin is being used as last resort treatment for life-threatening infections caused by carbapenem resistant Enterobacteriaceae (*E.coli*, *Klebsiella*, etc). Resistance to colistin have also been documented in several countries.

Endogenous and exogenous flora during pre- and post-surgical hospital stay is responsible for surgical site infections. This may include resistant organism present on the patient's skin, mucous membranes, viscera, theatre room, including air, equipment, materials, and staff members.

Due to the widespread use of broad-spectrum antibiotics, increasing rate of high virulence resistant organisms are usually isolated from post-operative wound infections.

Non-responding surgical site infections are likely to complicate healing of wound, cellulitis, abscess formation and osteomyelitis.

It may also lead to systemic complications, including bacteremia and sepsis. It becomes pertinent to focus on prophylaxis or prevention of SSI because treatment of SSI caused due to resistant microorganisms is becoming increasingly challenging.

Rise of antibiotic resistance has been observed in up to 46 per cent of low- to middle-income countries.

#### **Steps to curb AMR in hospitals**

The world is dealing with paucity of new antibiotics; only a few are in pipeline. Antibiotic shortages are affecting both the developing and developed world.

Optimisation of antibiotic management by surgeons to improve clinical outcome is the need of hour. Misuse and overuse of antibiotics should be discouraged in clinical practice.

Systematic approaches for the optimisation of antibiotic use in surgical settings, both for prophylaxis and therapy, should be undertaken. Hospital-based programs such as antimicrobial stewardship programs need to be incorporated for rational use of antimicrobials.

Active surveillance of SSI along with feedback should be provided to surgeons or hospitals to device their hospital infection control or antibiotic policies.

Global or national guidelines to prevent surgical site infections should be adhered to in all surgical settings. Preoperative modifiable risk factors that can lead to or complicate SSI like diabetes, smoking, immunosuppression drugs, etc must be taken care of prior to surgery.

Intraoperative risk factors like prolonged surgery, asepsis and surgical technique, hypoxia, hypothermia, poor glycemc control also contribute towards SSI and should be dealt with promptly.

Antibiotic administration of an antimicrobial for surgical prophylaxis one hour prior to incision is considered appropriate and effective in preventing SSIs. This allows tissue concentrations of drug to reach therapeutic levels at the time of operation.

Guidelines recommend use of narrow spectrum antibiotics, such as cefazolin for most surgical procedures, or ceftioxin for abdominal surgery for prophylaxis of SSIs.

Continuation of routine prophylactic antibiotics beyond 24 hours after surgery needs to be avoided. The selection of antibiotic, the dose, timing and duration of prophylactic medication is crucial. Use of wound protector devices post-surgery reduces the risk of SSIs.

#### **Coordinated action at global level**

Global Action Plan on Antimicrobial Resistance was laid out in 2015 during the World Health Assembly to improve awareness about AMR as well as to strengthen knowledge through surveillance and research.

The World Health Organization launched the Global Antimicrobial Resistance and Use Surveillance System in 2015 to continue filling knowledge gaps and to inform strategies at all levels. In 2017, WHO developed the priority pathogens list which will be updated in 2022.

Another landmark venture, Global Antibiotic Research and Development Partnership, aims to develop and deliver five new treatments that target drug-resistant bacteria by 2025.

Awareness and knowledge towards menace of AMR, especially in surgical settings, needs to be developed among surgeons world over. A gap analysis should be undertaken to compare the current practices with recommendations in guidelines for prevention of SSI.

Rational use of antimicrobials in practice is the key to overcome problem of antimicrobial resistance.

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## How to develop a template for community action on AMR

*ReAct Asia Pacific is engaging community stakeholder groups to mainstream action on antibiotic resistance*

By Philip Mathew

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The issue of antibiotic resistance (ABR) still remains invisible for the general public and the information on community-level drivers of ABR has not been collected and compiled. There is minimal incentive for governments and policy-makers to move forward on this issue.

I work for an organisation called ReAct Asia Pacific. We are working to develop pilot programmes, harvest learnings / insights from the implementation of ABR interventions on the ground and design tools for use by various community stakeholder groups.

We have designed an indicator framework to look at the issue of ABR through a 'One Health' lens, helping to quantify the drivers of ABR and look at the ground-level impact of the action plans.

Most of the National Action Plans (NAP) by countries were framed in response to the Global Action Plan on Antimicrobial Resistance published by the World Health Organization (WHO).

The mandates of several NAPs are ending in the next one year and multiple countries have started the process of framing the second edition of their action plan.

The approach taken by the first edition has mostly been top-down and local governance systems and communities were not involved in an optimal manner.

A bottom-up strategy is needed to complement the action plans, to make sure that there is sustainability and local resource mobilisation happening for ABR interventions.

We have started a qualitative evaluation of the ground-level impact of the first edition of NAPs in Vietnam and Bangladesh.

The studies showed that the NAPs have been unable to make a significant impact on the ground. Also, the novel coronavirus disease (COVID-19) appears to have taken away the political capital available for ABR interventions.

Various sectors continue to work in silos, even when the global narrative has been transformed over the years to advocate a more transdisciplinary approach to tackle complex issues like ABR.

The countries need to incorporate this understanding while framing the next edition of NAPs. Otherwise, it will remain as an exercise on the top.

We have also organised meetings with civil society and academia in these countries to disseminate the findings of the research.



This has been done to ensure they are aware of these issues and act as accountability mechanisms at the country level.

ReAct Asia Pacific has also been providing technical support to develop and implement state action plans in India. This year, we organised startup meetings in the states of Telangana and Meghalaya and the Union Territory of Puducherry.

The meetings were aimed at gauging the appetite for state action plans.

They also aimed at sensitising the various stakeholder groups at the state-level about the various interventions which are possible to contain ABR, especially in the background of COVID-19.

We also organised follow-up meetings to assess the progress of the existing state action plans and offer technical support wherever required.

It is important that the ABR community in India understands the entire value chain better to look at entry points for ABR action. This is because India is a hub for antibiotic manufacturing.

The understanding of the antibiotic value chain has interfaces with several ABR drivers.

These include optimal supply chain systems, optimal access to quality assured antibiotics, antibiotic pollution from pharmaceutical manufacturing and disposal of expired / unused antibiotics.

ReAct Asia Pacific has been working to design a visual guide to understand the antibiotic value chain — right from Active Pharmaceutical Ingredients to the disposal of antibiotics in hospitals and community settings.

The work, titled Journey of an Antibiotic, can help the policy community to understand the scope of ABR interventions and ways to strengthen the value chain.

Engaging students on the issue of ABR has been a priority for us, as they can be champions for behavioural change in the wider community.

We continued to engage college and university students through our ASPIC initiative and broadened the mandate to include school students too.

This year saw the publication of a training manual on ABR for high-school students, apart from a comic book directed at children.

We also facilitated an open letter to the WHO Executive Board on the need to have a policy to engage young people on the ABR issue and create a 'ring-fenced fund' for the same at the global level.

ReAct Asia Pacific has tried to fulfil its mandate by highlighting the need to prioritise ABR actions and bring in the 'behavioural change' perspective into action plans.

*About the author: Philip Mathew is a public health researcher and a consultant with ReAct Asia Pacific*

## Spreading awareness on medicine quality can be a solution for AMR

*Medicines must be manufactured according to high standards of quality and efficacy to reduce AMR risk*

By Chaitanya Koduri

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Antimicrobial resistance (AMR) is one of the most pressing global health challenges we are facing. Over 700,000 deaths are caused annually by AMR, according to estimates by World Health Organization (WHO).

AMR is predicted to kill two million people in India and 10 million deaths worldwide if nothing is changed to stop it.



Overuse of antimicrobials contributes to resistance. However, the quality of medicines and the way they are used also play a major role in this threat. Medicine quality can be compromised anywhere along the global supply chain, including quality assurance, manufacturing process, packaging integrity, storage and distribution conditions. When these factors are compromised, it contributes to the risk of AMR.

When patients are exposed to subtherapeutic levels of an antimicrobial, it increases their risk of developing resistant microbial strains that can cause deadlier infections. Nonadherence to prescribed medication has also been cited as a driver of AMR. Substandard and falsified medicines make patients who adhere to their treatment regimens vulnerable to antimicrobial resistance by exposing them to subtherapeutic levels of doses.

India has one of the largest burdens of drug-resistant pathogens in the world, particularly multi-drug resistant tuberculosis. Therefore, there is an urgent need to address this looming crisis.

### **Pandemics reinforce need to address AMR**

The novel coronavirus disease (COVID-19) pandemic has seen an overuse of antibiotics, both for empirical treatments and due to misinformation on the benefits of consuming antibiotics to prevent the infection.

But there has also been a significant increase in the availability of substandard and falsified medicines, including vaccines, during this pandemic. At the same time, widespread disease caused worldwide supply chain disruptions, while unexpected demand for certain medical products spiked, leading to shortages of extremely important medicines and critical supplies like personal protective equipment.

Together, all these factors increased the risk for AMR occurring as a result of poor quality medicines.

### **Poor-quality antimicrobials and AMR**

Ongoing research through USP's Quality Institute — a research collaboration of leading academic partners around the world — is helping establish that when medicines break down due to poor storage and distribution practices, have insufficient quantity of active ingredients or have unwanted impurities, it increases the risk of antimicrobial resistance.

Such low-level resistance can carry over across antibiotic groups and is difficult to detect clinically. The findings also have implications for patients who are exposed to products that may have become contaminated or degraded along the way in the supply chain.

### **'One Health' approach**

The principles and mechanisms of how quality issues in antimicrobials contribute to resistance are not sector-specific and may impact the use of microbials not just in humans, but also for the treatments of animals and use in agriculture. The 'One Health' approach requires coordination and collaboration across multiple sectors, including health care, environment, agriculture, and industry to ensure the appropriate use of quality antimicrobial medicines.

### **Potential solutions**

In order to reduce the risk of AMR, medicines must be manufactured according to high standards of quality and efficacy. Medicine quality assurance measures should be included in national action plans and key guidance documents for containing antimicrobial resistance especially for low- and middle-income countries.

Investments have to be made in regulatory health systems and country-level quality management systems to monitor substandard medicines. This should be done along with promotion of current good manufacturing practices and current good distribution practices to ensure antimicrobial medicine quality.

Policymakers in low- and middle-income countries, should understand the economic impact of poor-quality medicines and their role in the emergence and spread of AMR.

One of the primary components of antimicrobial stewardship efforts is to have the right medicine for the treatment of infections. Quality standards ensure that medicines have the identity, purity and potency as required by the regulations, thus directly aiding in stewardship efforts.

### **Scenario in India**

The Indian National Action Plan for AMR has robust language on medicine quality assurance and the stakeholder collaboration required for its implementation.

India has prioritised policies around tackling substandard medicines, given evidence that as much as 40 per cent of antibiotics like Gentamicin and Amikacin. Both these drugs are broad-spectrum aminoglycoside antibiotics and treat severe bacterial infections like meningitis.

As with many countries, progress on implementation has been slow. Although we see positive trends around collaboration among stakeholders, the emphasis on medicine quality as a contributing factor to AMR is low.

Investing in quality assurance of antimicrobials can result in a high rate of return and aim to mitigate AMR, reduce the burden of tuberculosis-resistant cases and achieve true universal health coverage.

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## Recent initiatives of DSPRUD towards AMR containment

*DSPRUD, a non-government organisation since 1996, has been working at various levels and contributing from policy to the grass root level with diverse stakeholders on AMR*

By Sangeeta Sharma and Renu Sharma  
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DSPRUD, a non-government organisation since 1996, has been a leading innovator, convener, partner and driver for introducing the concept of essential medicines and rational medicine use, especially antibiotics in India.



The Society is committed to focus and energise the essential medicines concept, rational medicine use and medication safety agenda to strengthen healthcare systems in both, the public and private sector.

Antimicrobial resistance (AMR), a major public health problem, has numerous biological, behavioural, economic, environmental and social factors contributing to its development and propagation.

DSPRUD has been working at various levels and contributing from policy to the grass root level with diverse stakeholders on the clinical and social dimensions of use / misuse of antibiotics, raising awareness about the impact of AMR and facilitator / barriers to promote rational antibiotic use.

Some of the important activities undertaken by the Society are listed below:

Policy level interventions

National Action Plan (NAP)-AMR, a top-level plan needs implementation at the state level and supplementation at the health facility level.

This is to successfully overcome the threat posed by AMR and to protect the effectiveness of existing and future antimicrobials.

DSPRUD played an instrumental role in the development of a multi-sectoral and multi-jurisdictional State Action Plan to Combat AMR in Delhi (SAP-CARD) in January 2020 with contribution from over 120 experts from the human and non-human sectors.

With this, Delhi became the third state to develop its own state action plan after Kerala and Madhya Pradesh. Besides, DSPRUD has been representing at the national level in National Working Groups on AMR.

### **Building capacity**

Initiatives tackling AMR, including state action plans, can only be fully exploited at the macro level by building the critical capacity for implementation of antimicrobial stewardship (AMS) interventions.

These should be well-integrated with infection prevention & control (IPC) at the hospital level.

The Society has been at the forefront of conducting training programmes for doctors, pharmacists and nurses to build skills for implementation of the AMS programme (AMSP).

They have developed an online certificate course on AMS in collaboration with Public Health Foundation of India (PHFI). The Society has so far conducted over 200 workshops and trained more than 8,500 health professionals.

### **Training on Antimicrobial Consumption (AMC) Tool and Point Prevalence Sampling (PPS) Methodology**

Both, the volumes of antimicrobial used and the prescribing practices contribute to the selection of AMR.

It is imperative that before initiation of any AMS activities, the magnitude of antibiotic use is measured and analysed to understand the causes of irrational prescribing practices followed by designing of interventions to rationalise / reduce the antimicrobial use.

DSPRUD is actively engaged in developing capacity in using AMC tools developed by the World Health Organization for the national surveillance sites (30 sites) under the National Centre for Disease Control (NCDC).

This is so that the AMC data provides the total quantum of antibiotics consumed and its trends for comparison.

### **Nurses as champions for IPC & AMS interventions**

Nurses being the largest workforce and in position as team leaders, can significantly contribute to the success of the AMSP. But their potential is less recognised and utilised.

Nurse-led AMS interventions can significantly improve antibiotic use practices by questioning an antimicrobial order, timely switching from IV to oral antibiotics or timely removal of catheter, etc.

IPC is a universal component of all health systems and integral to AMR containment.

The Society has played a key role in developing and updating standard operating procedures for IPC for Delhi hospitals since 2016 and running training / certificate courses for Infection Control Nurses on IPC, AMS interventions and critical care nursing. They have trained more than 1,300 nurses.

### **Developing Standard Treatment Guidelines (STGs): A Point-of-Care Clinical Support Tool**

Prescribing is a complex, dynamic process, influenced by many determinants. Inadequate training, combined with the lack of a functional antibiotic policy, are the leading causes of unchecked growth of AMR in Indian hospitals.

The availability and easy access to up-to-date guidelines for antimicrobial usage is an important pre-requisite for appropriate antibiotic use and improved patient outcomes.

The Society has been actively engaged in developing and implementing STGs at various levels of healthcare.

Our latest edition (2021), is a comprehensive evidence-based ready-reckoner covering 330 priority diseases developed and reviewed by a large number of experts.

It includes a section on AMS interventions and provides stepwise treatment of infectious diseases along with pearls for AMS. We are also conducting monthly online workshops in collaboration with ECHO India to train clinicians 'when not to use antibiotics'.

### **Patient / Public education / Community awareness**

Emergence of community-associated resistant organisms in the last decade has also highlighted the need of public awareness programmes as antimicrobials are consumed in a much larger proportion in the community, compared to hospitals.

DSPRUD has been actively working to design and implement community education programmes focusing on various aspects of antibiotic use by addressing misbeliefs / misconceptions about antimicrobial treatment, self-medication and poor adherence.

This is in pursuance of SAP-CARD Strategic objective 1.

Raising awareness about problems with antimicrobial use / misuse at a young age not only promotes behavioural change but also positively influences parental and community behaviour towards appropriate antimicrobial use.

The Society for the past two consecutive years has been organizing state-wide awareness campaigns among Delhi school students on the occasion of World Antimicrobial Awareness Week (WAAW).

In 2019, more than 600,000 school children from 1,041 Delhi government schools participated.

In the wake of the ongoing novel coronavirus disease (COVID-19) pandemic, WAAW 2020 campaign was conducted all online, wherein 3,500 teachers and 350,000 students participated.

Around 45,000 students took part in a quiz competition and more than 5,000 students participated in online 'IDEAthon'. Entries were independently evaluated and rewarded based on content, creativity / presentation and relatedness to the theme.

The Society is also committed to the cause of promoting rational antibiotic use, other activities include prescription audit and research into practices & factors in specific regional and local contexts and regular time-to-time assessment of the AMS programme in order to understand the existing structures, processes and outcomes.

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## Two crucial lessons for AMR on irrational antimicrobial use during COVID-19

*Antibiotic misuse was more in strained healthcare systems such as India during COVID-19 than in high-income countries*

By Nafis Faizi

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Azithromycin, Doxycycline, Faropenem, Amoxicillin / clavulanic acid, Cefixime. These are five of the many oral antibiotics that were rampantly misused in the novel coronavirus disease (COVID-19). If we add antimicrobials, hydroxychloroquine and ivermectin are the prominent additions.



None of them has been proven to work against COVID-19 per se. Repurposing drugs for use during the pandemic is a worthwhile scientific expedition if there exists some biological plausibility or evidence that it might work.

The WHO focussed on four such therapies, three of which were antivirals — Remdisivir, Lopinavir-Ritonavir and Lopinavir-Ritonavir with Interferon-alpha.

The other drug, an antimalarial — Chloroquine and Hydroxychloroquine were also on the list. All four of them were put under clinical trials for repurposing.

Chloroquine looked very promising. However, Chloroquine had shown such promises in dengue and chikungunya, among other viruses in the past. But the promises never came to fruition in the clinical trials.

Scientists had forewarned that it might be the same in COVID-19. But as none of them were antibiotics, there was no reason to believe that antibiotics would work against this novel virus. However, such therapeutic misadventures have continued since the first wave of COVID-19 in milder patients and skyrocketed during the deadly and devastating second wave of COVID-19 in India as well as other countries across the world.

Faropenem belongs to the 'Watch' group of antibiotics. It is a class indicated to be used only for limited infective symptoms and is more prone to be a target of antibiotic resistance.

COVID-19 is the most disturbing pandemic of our life. But, it has crucial lessons for antibiotic misuse in health systems. First, the crucial lesson concerning treatment guidelines. Adherence to standard treatment guidelines by healthcare providers is the fundamental pillar of evidence-based medicine.

Therefore, antimicrobial resistance (AMR) policies rightly focus on the stewardship of healthcare providers. However, the standard treatment guidelines (STG) need to be evidence-based, simple, non-ambiguous and locally relevant.

India's COVID-19 guidelines were slow moving and at times, not evidence-based at all. Ivermectin was prescribed or dispensed by states not only as a treatment but also dispensed to prevent COVID-19.

Such systemic misuse is not a matter of oversight. It reflects the disregard and indifference to processes and principles used in framing standard treatment guidelines.

This has crucial lessons for AMR. While STGs are an essential element of antibiotic policy at all levels of healthcare and need to be regularly updated, irregular updation or implementation could also prove counterproductive.

The feasibility and ease of use should also be an essential element of concern. A very successful example of a regularly updated guideline is eTG (now known as Treatment guidelines) from Australia, which is available on mobile phones and is accessible across all platforms.

India's expertise in digital health can be harnessed to make an easy-to-use application on antibiotic treatment which is regularly updated with updates from local evidence base. However, it also needs infrastructural support for local evidence generation, especially access to diagnostics.

Second, most antibiotic misuse is due to the absence of access to quality health care. That is why, during COVID-19, the oral antibiotics were more commonly misused, although evidence suggests that injectables such as Piperacillin-Tazobactam were also misused.

Among the higher antibiotics such as 'Penems,' the only oral form — 'Faropenem' was more commonly misused. Antibiotics were taken during those dire times as a prophylactic and precautionary measure as well as contrary to evidence and rationale.

While this seems like a one-off event, the process is similar to multiple instances of antibiotic misuse during many self-limiting illnesses, in the absence of access or affordability to healthcare.

Such antibiotic misuse in outpatient care is less in health systems with a better access to first point of care. This observation was consistent in COVID-19.

Antibiotic misuse was more in strained healthcare systems such as India, where one study found that "almost everyone who was diagnosed with COVID-19 received an antibiotic in India", whereas, at the same time, in high-income countries antibiotic use actually declined in 2020.

This also indicates that insurance-based, inpatient-focussed universal health coverage systems, will have little impact on antibiotic misuse. That is unless they are strengthened with a strong primary healthcare, with an improved continuum of care.

In India, prioritising and strengthening the health and wellness centres (HWC) as a first point of care could be essential in achieving this aim. The recently announced ABHIM (Ayushman Bharat Health Infrastructure Mission) in India, which aims to strengthen HWCs, could be a step in the right direction.

In conclusion, let's ponder over what Albert Camus wrote in *The Plague*, "No longer were there individual destinies; only a collective destiny, made of plague and emotions shared by all." The imperative of collective destiny is similar for both, the COVID-19 pandemic as well as AMR.

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## How vaccines can help reduce India's AMR burden

*The vaccine provides an indirect but significant benefit at scale to preventing the emergence of AMR*

By Jyoti Joshi

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The role of vaccines in the resumption of economic activities in India and other countries following lockdowns to contain the novel coronavirus disease (COVID-19) is fresh in our memory.

Thanks to the rapidly invented, licensed, manufactured and distributed COVID-19 vaccines, we are inching towards a new normal today. This is yet another illustration of the critical value of vaccines and their vital role in public health.



Next to drinking water, vaccines are the most cost-effective public health intervention in saving lives. Every year, vaccines avert 2-3 million deaths from diphtheria, tetanus, pertussis (whooping cough) and measles through their use in routine immunisation programmes globally, the World Health Organization (WHO) estimated.

In fact, the newer vaccines — pneumococcal conjugate vaccine and the *Haemophilus influenzae* type b (Hib) vaccine (in combination with DPT and Hepatitis B given as Pentavalent vaccine in India) — have collectively saved the lives of more than 1.4 million children under five years of age.

But these vaccinations have a major indirect benefit: Not only do they prevent these diseases, but they also prevent the development of antimicrobial resistance (AMR).

AMR is a simmering but silent public health emergency. It occurs when microorganisms (bacteria, viruses, fungi and parasites) evolve and stop responding to medicines, making even minor infections tough to treat, causing severe illnesses and deaths.

Every year 700,000 people die of antimicrobial-resistant bacterial infections, which will cause a loss of \$3.4 trillion to the world's annual gross domestic product in 10 years. Poor prescription practices, inappropriate antibiotic dispensing in pharmacies and self-medication practices are key determinants of AMR in India.

Antimicrobial resistance undermines the effectiveness of antimicrobials and stalls progress made against infectious diseases. Today, extremely drug-resistant pathogens, with resistance to all classes of antimicrobials, can be found throughout the world.

Rising resistance in some pathogens such as gonorrhoea (a sexually transmitted disease) has resulted in bacterial strains that are untreatable by the existing licensed antibiotics.

AMR threatens the vital progress made in improving quality of human life through joint replacement surgeries, cancer treatments and life support in intensive care units as the existing antibiotics become ineffective.

In a globalised world, AMR is everybody’s problem. The Global Action Plan (GAP) on AMR was launched in 2015 by WHO. Today, almost 80 countries have announced National Action Plans to address AMR at a national level.

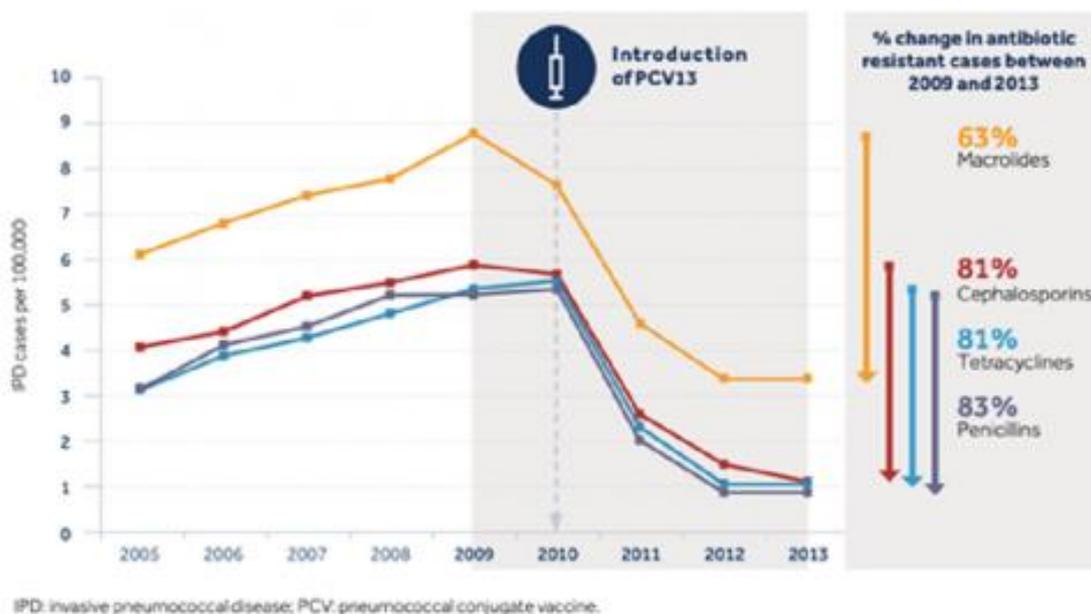
The GAP sets out the strategic objectives that include:

- Improving awareness and understanding of antimicrobial resistance
- Strengthening knowledge through surveillance and research
- Reducing incidence of infection
- Optimising use of antimicrobial agents in health, animal and food sectors
- Developing an economic case for sustainable investment that takes account of the needs of all countries
- Increasing investment in new medicines, diagnostic tools, vaccines and other interventions

Vaccines are a vital tool to protect people and societies from preventable infections and spread of disease-causing agents, whether resistant or not. Prevention of infections results in reduced use of antimicrobials for treatment, reducing the selective pressures that drive the emergence of resistance.

Reduction of AMR will lead to fewer untreatable infections and more lives. Vaccines such as pneumococcal conjugate vaccine (PCV) protect populations by preventing transmission of infection, and protecting those not vaccinated (“herd immunity”). This has been amply demonstrated by evidence from several countries, including the United States in the graph below.

Impact of pneumococcal vaccine on rates of drug-resistant invasive pneumococcal disease in the United States



Graphic: Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework

India is now among countries with the greatest number of deaths due to pneumococcal infection among children under five years. Modelled estimates suggest there are almost 1.6 million cases of severe pneumococcal disease in the country, with Uttar Pradesh and Bihar having the highest number of deaths.

India also has one of the highest antibiotic resistance rates among bacteria that commonly cause infections in the community and healthcare facilities.

The Universal Immunisation Programme (UIP) of India is one of the largest public health programmes, targeting almost 26 million newborns and 29 million pregnant women every year.

It has made key contributions in reducing infant deaths from 60/1,000 live births in 2005 to 34/1,000 live births in 2016. Within the UIP, the PCV vaccine was introduced in 2017 in select districts of Bihar, Uttar Pradesh and Himachal Pradesh.

The recent announcement to universalise PCV across the country is a welcome step for public health because of the collateral benefits.

Its availability free of cost to children in India protects not only the children from pneumococcal disease but also provides key protection to them and other population age groups from the emergence of drug resistant pneumococcal disease.

The vaccine provides an indirect but significant benefit at scale to preventing the emergence of AMR. As an AMR-sensitive intervention, it not only prevents pneumococcal disease in children (pneumonia, meningitis and other forms of invasive pneumococcal disease) but also decreases the selection pressure on circulating bacterial strains due to inappropriate antibiotic use.

However, to understand and quantify this benefit, it is important that research studies are instituted early on. Data must be collected on pneumococcal disease transmission, carriage, prevalent pneumococcal strains in India and their antibiotic susceptibility profile.

Improved surveillance at genomic level is vital as India expands PCV across the country. Such studies will provide critical data for effective resource allocation and help determine the success of such initiatives, while also informing the collateral benefit of the change in AMR profiles of pneumococcal bacteria in India.

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## A pandemic within a pandemic

*The use of antibiotics increased phenomenally during the pandemic; more than 70% patients were treated with antibiotics*

By Lakshmi Prasad, Jyoti Nath Modi and Sagar Khadanga

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The experience of COVID-19 times can be reminisced about in several ways. People went through unimaginable hardships. It has been a trying test of human resilience — as well as that of adaptiveness of healthcare systems across the globe.

Life came to a halt in several ways. The hallmark of civilisation, the transportation, too came to a grinding halt for quite some time. It is, however, commendable that the healthcare professionals, researchers, policymakers came together globally with an untiring effort to mount a response against this hitherto unknown pathogen to mankind.

The time is, therefore, apt for critical appraisal of the use — rather misuse — of antimicrobials against this virus.

Irrational and inappropriate use of antibiotics (and other antimicrobials) has been at the core of the increasing menace of antimicrobial resistance (AMR) globally. Hence, it is imperative that the use of antibiotics during the COVID-19 pandemic is thoroughly examined for its implications on AMR and mitigation strategies.

The use of antibiotics increased phenomenally during the pandemic. It is well acknowledged in the medical literature that more than 70 per cent of patients with SARS-CoV-2 infection (including those under hospitalisation and home-care) were treated with antibiotics.

The percentage was higher for the hospitalised patients and approached 90 per cent in the initial months of the pandemic in 2020. Needless to say, several millions of suspected (but not infected) COVID-19 cases must have consumed over the counter (OTC) available antibiotics at the first instance of the development of COVID-19-like illness.

At least half of these patients did not require antibiotics, and hence, had received them inappropriately. Such is the burden of misuse of antibiotics during the pandemic.

While it is easy to criticise such staggering figures of misuse, it is not helpful unless an effort is made to understand the reasons behind it, and take lessons from it for the future.

To begin with, antibiotics were used in these patients for two main reasons: One, the respiratory infection was treated as bacterial pneumonia before a confirmed diagnosis of SARS-CoV-2 infection



was made. This reason was especially true in the initial months of the pandemic when the disease was very new and poorly understood.

The elevated levels of C-Reactive Protein (CRP) that usually indicate a bacterial infection was also found to be raised in these patients, thereby clouding the diagnosis prior to confirmation by RT-PCR.

The second key consideration for using antibiotics was the evidence of, or the risk of bacterial co-infection, especially in elderly patients and those with co-morbidities. While these considerations sound reasonable, in reality, the antibiotics were used rampantly even for PCR-proven SARS-CoV-2 infection, even in non-hospitalised patients with mild disease, young people and in absence of co-morbidities.

This misuse was made worse by the easy and practically over-the-counter availability of antibiotics in low- and medium-income countries (LMIC).

The antibiotics that were most frequently used (or misused) since the early days of the pandemic were azithromycin, ceftriaxone, amoxicillin, piperacillin-tazobactam, meropenem, doxycycline, quinolones, etc.

The choice varied by the country or region, availability and inclusion in the protocol by various scientific bodies. However, some of these were used not so much for their antimicrobial action but rather for a possible antiviral and immune-modulator function. Azithromycin, meropenem, teicoplanin were some of such medicines.

While discussing the antibiotic use scenario in the COVID-19 pandemic in retrospect, it is not easy to fathom the effect of the panic created by such an unprecedented global situation on the clinical judgment and prescription practices of physicians.

Additionally, starting within a few months of the pandemic, the rapidly emerging evidence on the effectiveness of various therapeutic agents that was often contradictory and inconclusive only added to the confusion.

The treatment guidelines in various countries were being revised frequently in an effort to keep pace with the new evidence. To make matters worse, (at least during the initial days) no scientific community across the globe categorically denied usage of antimicrobials. Rather each country tried to figure which of the existing antimicrobial was best suited. This only compounded the misuse by the so-called literate healthcare community.

While we have limited our discussion to antibiotic use or misuse, the problem is compounded if we consider the use of other antimicrobial agents. The studies on hydroxychloroquine (HCQ) — an antimalarial and anti-inflammatory immunomodulator agent used in treatment of autoimmune diseases such as Rheumatoid Arthritis — is a burning example of the frail evidence-based medicine (EVM).

Former United States president Donald Trump bargained for HCQ with India; the same is still fresh in memory. The whole evidence for the basis of prescribing HCQ was withdrawn from literature as quickly as it was added into it. The same was true for many other antimicrobials.

Many LMIC countries lost out because of the resource crunch. The same is true for antivirals (lopinavir-ritonavir, remdesivir, favipiravir, etc), or antiparasitic agents (ivermectin) during the pandemic.

The horrific pictures of COVID-19-associated mucormycosis are also fresh in our collective memory. Most drugs were out of the market and the healthcare community was forced to prescribe inferior agents. Such was the chaos that COVID-19 patients were prescribed prophylactic anti-fungals.

The implications of use (or misuse) of antimicrobials are far-reaching. The short-term problems relate to the increased burden of allergic reactions, opportunistic infections such as candida, drug-induced metabolic effects and so on. The long-term consequence is a devastating increase in AMR with the global health impact.

The AMR pandemic was already a key priority area for attention as recognised by the World Health Organization and supported by the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).

The rampant antibiotic use during the COVID-19 pandemic has undone much of the progress made to get over the AMR pandemic since 2015. Active and urgent efforts towards instituting and enforcing rational use of antimicrobials in practice are an imminent need of the hour.

Antimicrobial stewardship should be an integral part of planning and response during a pandemic. This is perhaps the most important feed-forward for healthcare workers as well as policymakers.

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## How rethinking communication can go a long way

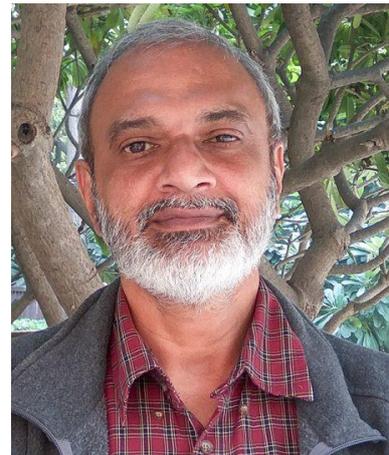
*People across demographics cannot be targeted as one group while spreading awareness*

By Satya Sivaraman

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There is a famous two-line poem in Hindi which, roughly translated, says, “In the vision of a cobbler, the entire Universe is a pair of shoes”.

To paraphrase in the context of medical professionals, “In the vision of a doctor, the entire Universe is a hospital”.



This is a good reminder for all those trying to communicate the complex issue of antimicrobial resistance to the rest of the world, to think beyond their narrow area of specialisation, understand their audiences better and pay more attention to context.

What do patients already know, what is it that they want to know or not want to know? What is the validity of the cultural, social, economic assumptions or teaching methods that we are basing our health messaging on? How should one communicate in order to get the message across in a meaningful way?

For example, among the interventions typically suggested for lowering antimicrobial use in different settings are regulation of antibiotic sales, avoiding inappropriate use and conservation of these medicines for only those critically in need.

Behind these suggestions is the assumption that strong policies, if combined with efficient implementation, training and adequate dissemination of information, will be sufficient to achieve the objectives of behaviour change needed to lower antibiotic use.

This is a classic top-down approach, where the experts believe their pronouncement of the truth will automatically lead to behaviour change. However, it cannot be assumed that any one conception of ‘health’, ‘disease’ or ‘medicine’ — even if it is the most ‘rational’ and ‘evidence based’ — should necessarily be accepted by the vast and diverse populations of the world.

The infant, the young, the elderly, the men, the women, the rich, the poor, the indigenous, the urban and the rural cannot all be put in the same petridish to be examined under a lens with the hope of arriving at one general formula for intervention.

There is simply too great a diversity of health-seeking behaviour out there for such one-size-fits-all formulas to work effectively.

Worldwide, there are many examples of interventions failing to make any impact or certainly being well below optimum in their results due to lack of understanding of cultural context.

The Union Ministry of Health in India, for instance, started a ‘red line’ campaign a few years ago to warn about the use of antibiotics without prescriptions. Under this campaign, there is a red colour line drawn on the packaging of antibiotics whose use comes under the highly restricted category.

The problem though is that 'red' is not a colour that signifies danger or serves as a warning in much of the Indian context. On the contrary, it is seen by large sections of the Indian population as an auspicious colour — used to mark positive events or objects. Indian women, and those around South Asia, wear red 'bindis' on their foreheads as part of tradition.

Surely, they are not a sign of impending danger! (Maybe this cultural fact is also one of the reasons why most Indian drivers refuse to stop their vehicles when the signal turns red!)

In the field of health communication in particular, the knowledge of cultural markers, beliefs and practices are essential. This is because, beyond their biological functions, medicines take on other meanings and roles in different arenas.

Anthropological studies in many societies around the world have shown how medicine is also historically associated with magic and faith, rendering them often beyond the pale of facts, evidence-based discussions and 'rational' prescriptions.

Again, much of the inappropriate use of antibiotics, whether in the human or health sector, is also driven by various powerful structural factors, particularly economic ones.

Unfortunately, the modern medical system, supposed to be based on sound principles and evidence, is heavily influenced by the quest for monetary profits by sections of the medical and drug industry.

The lure of money is such that sometimes regulators, practitioners and researchers are willing to tailor their policies, prescriptions and findings to suit the needs of the market, compromising even the science of modern medicine.

Similarly, the relation between doctors and patients or the public is a complex one and not entirely reducible to a simple equation of a health professional interacting neutrally with a health-seeker. There is money involved in this transaction too, which makes objectivity even more difficult.

Getting beyond all these confounding factors and still communicating effectively about the different dimensions of AMR is not an easy task.

However, it is a challenge worth undertaking given the severe consequences for everyone, as we saw in the case of the novel coronavirus disease (COVID-19), if this phenomenon is allowed to spread unchecked.

*About the author: Satya Sivaraman is a communication advisor to ReAct Asia-Pacific, which is part of a global network of academic institutions and civil society groups working on antimicrobial resistance.*

## How civil society works with government to contain AMR in Nigeria

*The participation of civil society organisations in veterinary service delivery is imperative for a huge country such as Nigeria*

By Dooshima Kwange  
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A Fulani family with their cattle in Nigeria. Photo: istockAntimicrobial resistance (AMR) has become a global threat to public and animal health as well as the environment. This necessitated the tripartite to develop the Global Action Plan on Antimicrobial Resistance.



Member countries were also encouraged to develop national action plans. Nigeria developed the National Action Plan for Antimicrobial Resistance (2017–2022) and the plan is currently being implemented.

Nigeria has a land mass of 923,768 square kilometres and a population of about 213 million. The governance structure is a three tiered system — federal, state and local government levels.

Due to several factors such as climate change, intensive animal production and urbanisation among others, the interaction between animals, humans and their shared environment has increased. Thus, there is a high disease burden in both humans and animals and several of the conditions are zoonotic.

A large proportion of the people and livestock farmers live in rural areas where healthcare service delivery is minimal and accessing health care services (laboratory diagnostic service, treatment, inputs) is a challenge.

Invariably, drugs are bought and administered without recourse to a healthcare professional. In animal production, the use of antimicrobials for growth promotion, coupled with lack of observance of withdrawal periods are also factors that drive AMR.

Monique Eloit, the director-general of the World Organization for Animal Health (OIE), says that to contain AMR: We sectors and countries all share responsibility in the development of antimicrobial resistance. It is by addressing this global threat together that we will manage to protect human and animal health, and therefore, our future.

This means all stakeholders including civil society organisations (CSO) have a role to play in mitigating the scourge of AMR. Thus, CSOs can work in collaboration with government and other stakeholders to contain AMR even with increased food production and also to preserve the much-needed antimicrobials for now and for the future.

### **Justification**

In Nigeria, there is paucity of trained animal healthcare professionals in the rural areas where most of the small holder farmers and producers live and access to quality healthcare service delivery is deficient.

The CSOs, which are non-state, not-for-profit organisations thereby fill the gap of weaknesses and take up the challenge of opportunities of government services that are provided to the public especially those in the rural areas.

There are fewer international, national and local CSOs within the animal health (AH) sector in Nigeria, compared to the public health sector.

### **Experiences from Nigeria**

CSOs therefore collaborate with government towards sensitisation of stakeholders, development and shaping of policies, provision of healthcare services, good governance, training of intermediate and lower level personnel among other activities. The CSOs are a link between government and beneficiaries of services.

In the Nigeria context, with a focus on AH, CSOs are working with the government in the following areas to contain AMR.

- Awareness/Advocacy

The threat of AMR is often times not easy to communicate due to the fact that there is low risk perception and the negative impact is not felt immediately in most cases.

Consequently, CSOs have collaborated with the implementing agencies such as the department of Veterinary and Pest Control Services of the Federal Ministry of Agriculture and Rural Development, Nigeria Centre for Disease Control and Federal Ministry of Environment to sensitise the public through rallies and walks, talks on television and radio programmes as well as advocacy visits to policymakers during the World Antimicrobial Awareness Week.

During the 2019 WAAW, a special session was held at which various top-level officials in ministries, departments and agencies (MDAs) and the national assembly took the AMR Guardian pledge. In the animal health sector, visits to livestock / live bird / fish markets, abattoirs and schools were conducted.

- Evidence

The CSOs have conducted retrospective studies and situational analysis to bring out data in support of development of new policies and legislation. This is crucial in light of the paucity of data for AMR especially within AH.

One such policy is prohibition of the use of antimicrobials for growth promotion in food producing animals. Presentations have been made at various fora on the availability and use of alternatives to antimicrobials and the outcomes in agriculture.

- Provision of services and inputs

Services provided by CSOs include provision of thermos-stable Newcastle vaccines produced by the National Veterinary Research Institute to farmers in rural areas for use in scavenging chickens, subsidised animal drugs from manufacturers to farmers thereby removing the middlemen and ensuring availability of good quality products.

- Capacity building

There have been training sessions of community AH workers in a collaboration between state governments, the Veterinary Council of Nigeria and CSOs.

This is to build the capacity of middle and lower level manpower and thus bridge the gap in the availability of animal health care personnel in the rural areas.

There are also discussions ongoing about institution of the sanitary mandate programme in the PPP setting. Some CSOs have trained producers in the aspects of biosecurity, record keeping and good management practices.

Many CSOs have hosted webinars for sharing of information and knowledge to different stakeholders sometimes in the One Health approach.

- Mobilisation of funding

CSOs are well-placed to source and mobilise funds from donors for mitigation of the AMR threat as there is less bureaucracy to navigate. Also, in most cases, especially for the national / local CSOs which are smaller organisations, such funds and the deployment of the resources can be better tracked.

### **Conclusion**

For CSOs to be effective, they must be responsive, transparent, accountable and align themselves with the overall goals of the government concerning the sector of interest.

This will enable them to gain the trust and cooperation of the government and the people they seek to serve.

Some of the challenges of CSO operations are the issue of sustainability, retention of skilled manpower especially when funding wanes and dependency on donor funding. Nonetheless, participation of CSOs in veterinary service delivery is imperative for a huge country such as Nigeria.

*About the author: Dooshima Kwange is CEO of Tesedona Foundation for Animal Health in Nigeria*

## How poor regulation threatens aquaculture

*There are no regulations or institutional setup for freshwater aquaculture*

By T. J. Abraham

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Aquadrugs in fish, shrimp culture: Poor regulation threatens ecosystems with anti-microbial resistance.

Aquaculture is the world's fastest-developing food production sector and represents an important impediment to food production. Fish are the most-traded food commodity in international trade with an export value of nearly \$150 billion (around Rs 11.2 lakh crore).



The globalisation of aquatic animal products and the rise of aquaculture as a primary supplier of the world's aquatic food supply have led to an intensification of culture practices. This has created new market opportunities for farmed aquatic animals but has simultaneously facilitated the easier spread of pathogens and diseases.

Diseases are a primary constraint to aquaculture and a variety of drugs are used to control the diseases. However, the imprudent use of these drugs in aquaculture is a contributing factor in the spread of anti-microbial resistance (AMR). Continuous use of antibiotics for alleviating bacterial diseases in aquaculture has led to 'pseudo-durability' and their omnipresence in the environment, which has caused the development of selective pressure on the microbial community.

Antimicrobial-resistant bacteria (ARB) formed under selective pressure can develop into an environmental reservoir of antibiotic-resistant genes. Aquaculture systems and fish farms have been observed as the 'hotspots for AMR genes' and hence the assessment of resistome, the AMR gene assemblage in aquaculture, is an important topic of research worldwide.

Since the majority of antimicrobials used in aquaculture are also employed in human medicine, their use has a significant impact on the development of AMR in other ecological niches, particularly the human environment. Researchers have reported an increase in the frequency of serious infections and treatment failures as a result of antimicrobial resistance being transferred from aquaculture to humans through the consumption of aquaculture products.

Aquaculture in India, particularly shrimp and carp aquaculture, has been playing a significant role in the agriculture sector. Misuse and overuse of antibiotics are pervasive in both brackishwater and freshwater aquaculture.

The use of aquadrugs is common in major fish-producing states like Andhra Pradesh and West Bengal. The use of antibiotics is slowly rising in states like Bihar, Jharkhand and Odisha.

There are standards, guidelines and an institution to manage the use of antibiotics and pharmacologically active substances in export-oriented brackishwater aquaculture. But there are no

regulations or institutional setup for freshwater aquaculture, which account for two-thirds of India's fish production.

In other words, while we are protecting the health of our export customers, we have no concern for domestic consumers.

Besides food-fish production, antibiotics have got large scale applications in ornamental fish production. In recent years, the increased development of ornamental fish culture in many states has opened up problems of disease and water quality deterioration in ornamental fish.

Most of the ornamental fish varieties are normally procured from neighbouring Asian countries to India mainly through legal and illegal means. Ornamental fish have been the source of exotic bacterial and viral pathogens that have mandated strict quarantine regulations.

A wide range of antimicrobials have found their way into Indian ornamental fish culture since there are no strict guidelines in ornamental fish. Most of the aquaculture farmers are small-scale entrepreneurs with farm sizes less than two hectares. This creates a situation where the farmers may not be able to afford the investment needed to install biosecurity measures in farms.

Most of the shrimp farms get their seed from bio-secured hatcheries. However, several antibiotics are used at the time of transport with an erroneous assumption that they can reduce the mortality in seeds during transportation.

#### **Poor regulation**

A large part of the antibiotic use is not supervised by any scientific personnel and is generally based on the experience of fellow farmers. The policy of the European Union to reject consignments of shrimp, which has the presence of antibiotic residues has had a definite impact on the use of antibiotics in shrimp aquaculture.

The Marine Products Exports Development Authority is now conducting regular inspections of shrimp products, to ensure that it complies with export standards laid down by various international agencies. But this inspection is confined to the products meant for the export market and those meant for local consumption is largely unregulated.

Farmers have brought down the use of antibiotics through several biosecurity measures. There is very little antibiotic use in cage farming due to the complexity involved in administration. But in aquaculture farming other than shrimp, there is significant use of antibiotics. This is because the products are meant for local consumption and the market is highly unregulated.

In integrated farming, poultry waste and bird droppings are used as fish feeds. This gives rise to a peculiar situation in which there is antibiotic contamination of the aquaculture environment, even without direct use of antibiotics since poultry farming uses a high amount of antibiotics.

*Vibrio* bacteria has been isolated from coastal aquacultural areas showing a high prevalence of AMR. *Aeromonas* spp (species plural) depicting multi-drug resistance (MDR) have been isolated from the freshwater aquaculture systems.

The southern states of India, particularly the wetlands of coastal Kerala, Tamil Nadu and Andhra Pradesh, are considered to harbour high levels of ARB. Two-thirds of the samples drawn from fish and shellfish obtained from the markets have Salmonella strains resistant to at least two antibiotics.

These results reflect the poor implementation of the existing legislative provisions, as well as the polypharmacy practised in the aquaculture sector. Such emerging AMR and MDR rates in India are an alarming situation.

The Food Safety and Standards Authority of India has placed an extensive ban on the use of antibiotics and several pharmacologically active substances in fisheries. The long-term impact of the use of antibiotics for aquaculture not only has ramifications for the emergence of resistance in indigenous bacteria but also has a yet unmeasured impact on the ecology and the environment.

Due to the existence of stringent legislative provisions to contain the inappropriate and non-therapeutic use of antibiotics, it is expected that the problem of AMR in the aquaculture sector should be smaller compared to other sectors. However, the monitoring and implementation lack a roadmap, making it difficult to form a policy.

There is an absence of a 'One Health' approach to AMR containment at a policy level, as the focus is more on human health issues and the scope of the problem in the veterinary and aquaculture sectors, although acknowledged, is not outlined in granular details.

Few regulations and legislative measures are available against the non-therapeutic use of antibiotics in food animals. Limited legislations are available for the control of antibiotics in the livestock sector, although some legislative tools are available for fisheries and poultry raised exclusively for export.

Improving hygiene, using enzymes, probiotics, prebiotics and acids to improve health and utilising bacteriocins, antimicrobial peptides and bacteriophages as substitutes for antibiotics might be good methods to promote fish growth and decrease infectious diseases in them. As of now, stringent monitoring on antimicrobial use in Indian aquaculture is deemed necessary for the betterment of human health and aquaculture.

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## Antibiotic use trends in Mozambique's veterinary sector and efforts to contain it

*The country imports most of its veterinary antibiotics from the Netherlands, India, Argentina, South Africa, France and China*

By Fernando Rodrigues

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Antibiotic Use trends in Veterinary Sector in Mozambique and Efforts to Contain it Photo: Stevie Mann / Wikimedia Commons

In recent years, the growth and expansion of veterinary activity has been verified throughout Mozambique. This came with the consequent proliferation of establishments that provide veterinary assistance services as well as the sale of veterinary medicines and products due to the increase in livestock numbers, particularly the poultry farming area by the family sector.

This sector has limitations in the observance of Good Production Practices, from the point of view of biosafety in its facilities. Thus, the occurrence of infections is frequent, which requires the use of antibiotics.

The authorisation for the entry of medicines for veterinary use in the country is preceded by the registration of the company at the Ministry of Agriculture and Rural Development and application for an import license at the Veterinary Authority. The import of Veterinary Medicines is done by the private sector, following the requirements set out in the specific legislation.

The main international companies supplying pharmaceutical products to Mozambique are Aviourem Specialities Pharmaceuticals, Bayer, Bupo Animal Health, Interchemie Werken, Intervet, Kepro, Kyron Laboratories and MSD Animal Health.

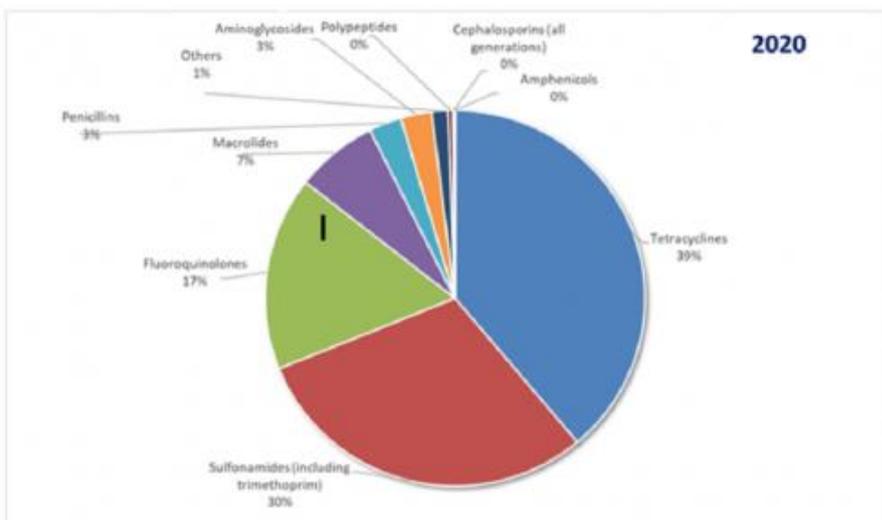
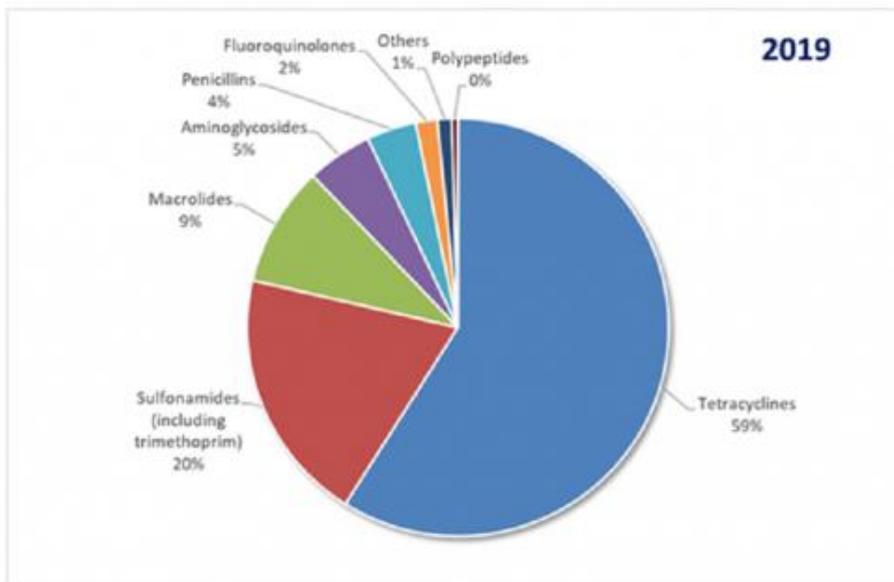
Most imported antibiotics come from the Netherlands, India, Argentina, South Africa, France and China.

The active principles of the most imported antibiotics are oxytetracycline hydrochloride, sodium sulfadiazine, doxycycline hyclate, erythromycin thiocyanate, tylosin tartrate, sodium sulfaquinoxaline, streptomycin sulfate, penicillins and enrofloxacin. All of them are intended for animal use. Oxytetracycline hydrochloride is imported the most.

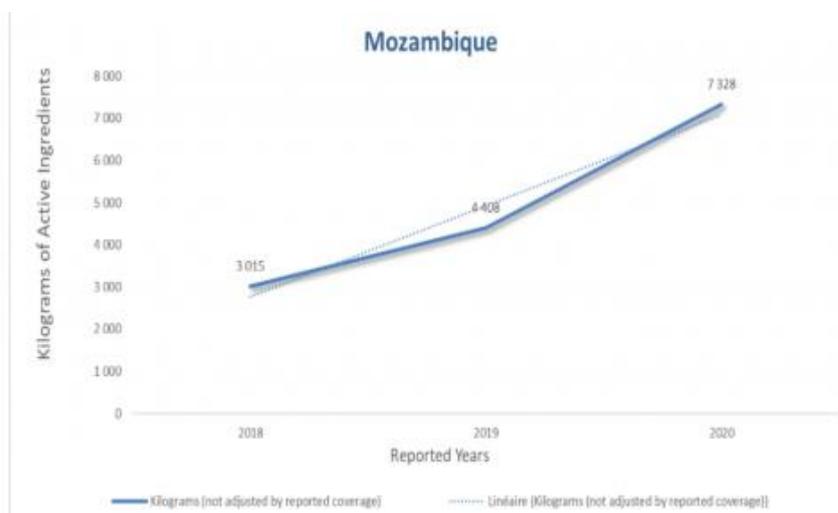
Regarding antibiotic classes, the largest import is made up of the group of tetracyclines, sulfonamides, penicillins and macrolides.



## Classes of antibiotics imported into Mozambique



Source: World Organisation for Animal Health (OIE)  
Total active ingredients imported into Mozambique (2018-2020)



## **Efforts to contain use**

The country has normative instruments aimed at the control and prudent use of antimicrobials, some of which are in force and others still awaiting approval by competent authorities.

### **1. National form of veterinary medicines**

It is a normative instrument that describes essential veterinary products, designated by the following:

- Generic names or international common denomination
- Recognised pharmacological classification
- Active principles
- Route of administration
- Indications of the target species
- Dosage
- Contraindications
- Side effects
- Other important information for the knowledge of users.

Its purpose is to serve as a practical tool for consultation by professionals with a view to the correct administration of drugs to animals.

In general, only medicines, including antibiotics, mentioned in the National Form of Veterinary Medicines may be authorised to be manufactured, imported, distributed and sold in the country. Currently, this form, dated 1986, is in the process of being updated.

### **2. National action plan against antimicrobial resistance (AMR)**

The plan was developed following the “One Health” approach, a multi-sectoral effort among the areas of human, animal, environment, fisheries, agriculture, academic and research institutions, professional associations and cooperation partners.

The vision is to ensure the rational use of antimicrobials in humans, animals and reduce the presence of antimicrobials in the environment. This plan has six strategic interventions to control AMR, through improvement in both prevention and access and use of antibiotics for humans and animals:

- I. Improve awareness and knowledge of AMR, and educate public and animal health professionals
- II. Reduce the incidence of infections through effective vaccination, sanitation, hygiene and prevention as well as infection control
- III. Strengthen knowledge through surveillance, and ensure sustainability through funding and research
- IV. Improve access to antibiotics to treat infections
- V. Optimise the use of antibiotics in human and animal health
- VI. Change incentives that anchor the overuse of antibiotics and enforce their rational use

An important aspect for the reduction of indiscriminate use of antibiotics is to systematically and continuously strengthen the training of animal health professionals in AMR matters, with an emphasis on antibiotic administration programs combined with rapid diagnostic technologies. It is also important to invest in the vaccination of livestock and in the prevention and control of infections to reduce the consumption of antibiotics.

### **3. Animal health regulation**

In compliance with this regulation, the use of hormones and growth promoters in animal production, including antibiotics, is prohibited.

### **4. Regulation of drugs, medicines and veterinary products proposal**

It provides for aspects related to dispensing, which assumes that drugs, medicines, including antibiotics and veterinary products subject to veterinary prescription and intended for farm animals, can only be dispensed to the public with a veterinary prescription.

### **Other government efforts**

In order to ensure greater technical guidance to breeders who buy medicines, all establishments that sell veterinary medicines, including antimicrobials, must have a technical director, a veterinarian, registered in the veterinary statutory body of Mozambique.

A One Health Platform was established in the country, with two working groups — one for zoonosis and the other for AMR.. The AMR group is composed of three sub-groups: Prevention and control of infections; optimization of the use of antimicrobials (stewardship); resistance to antimicrobials.

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## Some possible solutions to reduce antibiotic dependence in aquaculture

*Antimicrobial resistance is a multi-driver problem and only a multi-thronged approach can be helpful in tackling this scourge*

By Mukteswar P Mothadaka

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Fisheries is the only food sector that has shown continuous growth in India, surpassing all other sectors catering to the food and nutritional security needs of hundreds of millions.

Fish is also an important source of animal protein that is available at an affordable price to all classes of people including economically underprivileged groups and those in the hinterland.

The population of the country was 1,398,880,820 at 23.47.20 hrs on November 13, 2021. It is predicted to increase to 1,639,176,033 by 2050.



Food demands need to be met in unit time and space and fisheries is the only sector that can help, provided that threats such as antimicrobial resistance (AMR) are done away with.

Antibiotic resistance is a serious threat to aquatic animals in terms of disease resistance that is beyond control. It can seriously impact productivity, is a human health hazard and also harmful to the environment.

Aquaculturists are in a perennially paradoxical situation as they are forced to increase productivity by increasing stocking density which results in stress to aquaculture animals.

It makes the animals prone to diseases and the need for application of antibiotics at different stages.

### Possible solutions

Here are some of the possible solutions with which the dependence on antibiotics can be reduced:

**Good aquaculture practices:** Sustainable fisheries that do not have the residues of antibiotics due to AMR are the need of the hour. This is possible with a general action plan that includes biosecurity measures.

**Probiotics:** The role of probiotics is undeniable in paving a successful path for gut health and environmental quality in aquaculture. In the present-day scenario, many probiotics are available for aquaculture, including *Bacillus* spp, lactic acid bacteria, yeast and nitrifying / denitrifying bacteria.

**Prebiotics:** Prebiotics are the foremost eco-friendly feed additives in the aquaculture industry.

The presence of beneficial bacteria in the guts of fish results in fermentation and the byproducts are prebiotics that help in improving the health of aquaculture animals. A healthy animal free from diseases does not necessitate application of antimicrobials, thus preventing development of AMR in aquaculture.

**Botanical products with antimicrobial activity:** Reports indicate that plant extracts can act as eco-friendly deterrents against bacterial fish disease, with a success rate of 83 per cent and can successfully eliminate pathogens like *Aeromonas hydrophila* and *Streptococcus agalactiae*.

**Seaweed extracts:** Their application can result in the improvement of immunity and additional physiological performances among aquaculture animals. These benefits have been well-documented.

**Antimicrobial peptides:** The antimicrobial peptides of fish have significant effects on the inborn resistant mechanism reaction of teleost fish and are recognised as the primary, first line of defence against a wide range of pathogens.

**Exclusion of aquaculture therapeutants by carbon absorption:** Carbon absorption treatment to eliminate therapeutants without causing stress to the fish stock is very much possible.

**Enzymes in aquaculture:** Enzymes employed in aquaculture such as proteases, amylases, cellulase, esterase, lipase, urease and xylanase are intended to enhance the availability of nutrients and help nutrient absorption in the digestive system. The end results are faster growth rates and healthy fish that support aquaculture free from antibiotics.

**Organic acids in aquaculture:** Reports indicate that nutritional supplementation of citric acid to plant protein based-diets is most effective in improvement and maintenance / accessibility of minerals, especially phosphorous. The use of sodium butyrate too has given very encouraging results in changing the intestinal microflora of catfish and shrimp.

**Minerals usage in aquaculture:** Minerals such as chromium, cobalt, copper, iodine, iron, manganese, molybdenum, selenium and zinc play a very important role in the upkeep of osmotic pressure and therefore normalise the exchange of water and solutes within the animal body. Minerals function as structural components of soft tissues.

**CLA in aquaculture:** Conjugated linoleic acids (CLA) are useful in aquaculture. A study about the effects of CLA and curcumin (CUR) on growth performance and oxidative stress enzymes in juvenile Pacific white shrimp (*Litopenaeus vannamei*) feed with aflatoxins revealed that CLA and CUR supplementation is beneficial in protecting juvenile shrimp against aflatoxins. This indicates CLA improves immune function.

**Phospholipids:** In aquatic animals from both fresh- and brackish water sources, ideal growth, survival and the absence of deformities in the skeleton, especially in larval and juvenile fish, are crucial. In this context, the role of phospholipids is significant. In larval phases, the fish are vulnerable due to a dearth of phospholipids.

**Genetic switch:** Certain classes of gene regulatory networks exude bistable behaviour termed as a 'genetic switch'. This results in protein products of one gene expression being switched off.

The most common genetic switch products are surface antigens essential for adhesion, motility and cell-type determination such as flagellin, pilin, extracellular polysaccharide and  $\alpha/\alpha$  mating-type proteins.

This phenomenon can be used in aquaculture to control multiple drug resistant bacteria with RNA molecules. The use of altered RNA (riboswitches or riboregulators) result in down regulate resistance in bacteria, rendering them defenceless.

One such observation was the control of virulent genes using DNA Adenine-Methylase that exists in bacteriophages and bacteria that can decisively eliminate the resistant bacteria. This type of product helps in minimising the use of antibiotics in aquaculture.

**Bacteriocins in aquaculture:** One of the key tools in combating the menace of ARB (Antibiotic Resistant Bacteria) are bacteriocins, the antimicrobial peptides produced by certain bacteria, as significant alternatives to traditional antibiotics.

The advantage with bacteriocins is that they are stable and possess narrow or broad spectral activity. Bacteriocins are also formed in situ in the gut by probiotic bacteria to combat intestinal infections. One aspect that needs to be taken care of is gut bacteria themselves developing resistance.

**Bacteriophages in aquaculture:** Phage therapy in aquaculture is a viable alternative to antibiotics for the treatment of bacterial infections. The better choice in controlling bacterial diseases and the evasion phase resistance is the use of a cocktail of lytic phages.

The flipside is the conversion of non-virulent bacteria to virulent strains by lysogenic phages that can jeopardise food production and food safety. The need of the hour is food safety regulations for the use of bacteriophages to eliminate the possible spread of virulent genes.

**Quorum Sensing Inhibitors (QSI):** Quorum sensing (QS) is a mechanism of communication between bacteria. It comprises of QS signal molecules and regulatory protein components.

They control physiological behaviours and virulence gene expression of pathogenic bacteria. QS inhibition is thus a unique approach to fight pathogens and related diseases.

Broadly, QS inhibitors (QSIs) are classified as minor chemical molecules and quorum quenching enzymes are mined from marine and terrestrial environments.

In recent years, the focus has been on marine sources, starting with the screening of marine bacteria with potential QSIs. Voluminous data has been generated on the source aspects, structures, QS inhibition mechanisms, environmental tolerance, effects / applications and structural modification of natural small molecule QSIs for drug development in future.

Probable applications of QSIs from marine bacteria in aquaculture were explained, signifying capable and widespread application of QS disruption as an innovative antimicrobial strategy.

**Competitive exclusion (Nurmi-effect):** The process of normal healthy intestinal bacterial flora colonising the intestine and thwarting the establishment of pathogenic bacteria temporarily is called complete exclusion.

**Polyhydroxyalkonates (PHA):** The application of shortchain fatty acids and Polyhydroxyalkanoates decreases the pH of the intestine that in turn promotes the growth of LAB, colonising the gut, consequently hindering the proliferation of pathogenic bacteria.

**Nanoparticles:** The application of inorganic material in the food industry as additives will be a new pathway to overcome the development of multi-drug resistant pathogenic and spoilage bacteria.

Among inorganic materials, Zinc Oxide nanoparticles (ZnO-NPs) are considered as suitable food additives. The United States Food and Drug Administration has recognised Zinc Oxide (ZnO) as a generally safe material for food application.

ZnO-NP possess better antimicrobial properties than the bulk ZnO and exhibit strong activity even in small amounts. An added advantage is that they are stable at high temperature and pressure.

**Electron Beam Irradiation for removal of antibiotic residues:** Electron beam irradiation (EBI) is a non-radioactive, safe, easy-to-adopt and rapid method. Recently, EBI was used to destroy the antibiotics present in discarded medical intravenous devices, syringes and bottles.

The application of the EBI will be useful to degrade the antibiotics in water.

**CRISPR:** Bacteria have developed a unique defence mechanism called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) in RNA to ward off viral attacks. This technique has potential application in fisheries. It can remove pathogenic bacteria and AMR pathogens.

AMR is a multi-driver problem and only a multi-thronged approach can be helpful in tackling this scourge.

In 2019, the Food and Agriculture Organization established the AMR MPTF (Antimicrobial Resistance Multi-Partner Trust Fund). It recorded the progress in tripartite partnerships, national and global programmes and visualised the future scenario.

In view of the demographic vastness of India and the needs therein, the implementation of MPTF will surely lay a strong foundation for sustainable progress not only for antibiotic-free fisheries but other sectors too, namely environment, aquatic food safety and human health.

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## OIE initiatives for responsible, prudent use of antimicrobials in animals in Asia-Pacific

*The organisation conducted workshops to spread awareness & understand how antimicrobial use data can be shared among stakeholders*

By Kinzang Dukpa, Hirofumi Kugita, Ronello Abila, Lesa Thompson, Jing Wang, Supalak Prabsriphum and Tikiri Wijayathilaka

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The World Organisation for Animal Health (OIE) was established in 1924 in response to the need to fight animal diseases at global level. It is the intergovernmental organisation responsible for improving animal health worldwide and currently has 182 members.

OIE has been addressing antimicrobial resistance (AMR) for many years. In 2016, it launched The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials that has four key objectives of enhancing awareness and understanding, strengthening knowledge through surveillance and research, supporting good governance and capacity building and implementation of international standards.

Contained in several chapters of the Terrestrial Animal Health Code and the Aquatic Animal Health Code, the OIE provides the latest scientific information on AMR, for terrestrial and aquatic animals that countries can use for AMR surveillance, monitoring of antimicrobial use (AMU) in animals and in implementing responsible and prudent use of antimicrobials. Chapter 2.1.1 of the OIE Terrestrial Manual provides laboratory procedures for antimicrobial susceptibility testing.

The OIE List of Antimicrobial Agents of Veterinary Importance, published in 2007 and last updated in June 2021, is divided into three categories: Veterinary Critically Important Antimicrobial Agents, Veterinary Highly Important Antimicrobials and Veterinary Important Antimicrobials. The list is for countries to implement responsible and prudent use of antimicrobials in livestock and aquaculture production.

Based on this list, the OIE recommends that fluoroquinolones, third and fourth generation of cephalosporins and colistin should not be used as preventive treatment in the absence of clinical signs, should not be used as a first line of treatment unless justified, to avoid using as extra-label / off-label unless no alternatives are available and urgently prohibits their use as growth promoters.

The OIE is mandated by the global tripartite to take a lead role in developing and maintaining the global database on AMU in animals (AMU database). The Asia-Pacific region is the highest consumer of antimicrobials (by animal biomass) as compared with other regions, according to the Fifth OIE Annual Report on Antimicrobial Agents Intended for Use in Animals.

The OIE has also developed several communication materials targeting stakeholders who have a role to play in addressing AMR in countries.

Armed with these standards, tools, guidance and reports, the OIE Regional Representation for Asia and the Pacific based in Tokyo, Japan and the OIE Sub-Regional Representation for South-East Asia based in Bangkok, Thailand have been implementing several activities to address AMR in the Asia-Pacific region.

To enhance awareness on AMR, we have been providing technical and financial support to many countries in the region to undertake advocacy events on AMR, especially during the World Antimicrobial Awareness Week held annually in November.

Since 2018, the organisation have supported countries such as Bhutan, Cambodia, Malaysia, Lao PDR, Myanmar, Mongolia, Nepal, Thailand, Timor Leste and Sri Lanka and Vietnam, in translating OIE's awareness materials into their national languages for use during the advocacy events.

China and Japan also translated OIE's awareness materials and used them for their advocacy events. As the bulk of the antimicrobials are used in livestock production, the organisation conducted workshops in Bhutan, Cambodia, Lao PDR, Myanmar, Philippines and Vietnam, targeting livestock and aquaculture producers, industries, veterinarians, animal health workers, aquatic animal health professionals, among others.

The use of OIE's standards as well as guidelines on prudent and responsible use of antimicrobials and encouraging public-private partnerships in AMR control was advocated.

OIE organised workshops targeting veterinary students and faculty members in veterinary schools in Bangladesh, Cambodia, India, Indonesia, Lao PDR, Myanmar, Philippines, Vietnam and Sri Lanka in 2018 and 2021. The aim was to make the veterinarians, veterinary paraprofessionals and aquatic animal health professionals aware of the organisation's standards and guidelines as well as AMR and how they can play their part in addressing the crisis.

The motive was also to encourage a professional culture which supports the responsible and prudent use of antimicrobials in animals. The seminars raised awareness on AMR and emphasised the need to include AMR in the veterinary education core curriculum of the veterinary universities.

In many countries in the region, regulations and monitoring of AMU in the animal sector is ineffective, largely due to a lack of coordination and data sharing among stakeholders.

Since 2018, the OIE has organised in-country AMU monitoring workshops in Bangladesh, Bhutan, Cambodia, Lao PDR, Malaysia, Mongolia, Myanmar, Nepal, Pakistan, Indonesia, Philippines and Sri Lanka to enhance monitoring of the quantities and usage patterns of antimicrobials used in animals.

The key output of such monitoring workshops is understanding the dynamics of antimicrobial usage in the animal sector in which countries can understand the flow of antimicrobials in terms of import, manufacture, distribution, usage and the stakeholders responsible for regulating at each level of the AMU supply chain.

The workshop brings together stakeholders who have a role in antimicrobial usage, including government regulators, private sector (manufacturer, importer, distributor, wholesaler, retailer), animal industries, livestock associations. The organisation seeks to understand what sort of AMU data each stakeholder can provide to the national regulatory authority for AMU monitoring.

Amid the global pandemic in 2020 and 2021, OIE adapted its activities and organised several webinars covering aspects on reviewing implementation of national action plans on AMR, AMR communication skills, and the AMU database.

Several challenges still exist in the Asia-Pacific region to implement responsible and prudent use of antimicrobials in the animal sector.

There is weak enforcement of legislation in regulating the import, production, sale and monitoring of antimicrobials used in animals.

There is inadequate supervision by veterinarians on the usage of antimicrobials in animals and that of antimicrobial agents as growth promoters in the absence of risk analysis.

Therefore, there is a need for continued action at all levels in addressing the threat of AMR through advocating as well as implementing responsible and prudent use of antimicrobials in livestock production.

The OIE will continue to work closely with its members in advocating responsible and prudent use of antimicrobials in animals in our quest to address AMR in the Asia-Pacific region.

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## Zoonosis as a driver for antimicrobial resistance

*The diseases which are naturally transmitted between humans and animals, are a major driver that can threaten human health by facilitating the emergence of AMR pathogens*

By H Rahman and Jagadish B Hiremath  
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Antimicrobials have been among the greatest of human discoveries. They have significantly increased the quality of life and life expectancy for humans and animals.

Intensive livestock farming with the goal of high economic returns employs all means to reduce the level of disease. One such measure is the use of antimicrobials as feed supplements or growth promoters.

In recent years, the use, abuse and misuse of antimicrobials in both, the human and livestock sector, has resulted in large-scale antimicrobial resistance (AMR) among various pathogens and more so, in bacterial pathogens.

Currently, AMR is a global challenge. It has forced international bodies such as World Health Organization, World Organization for Animal Health (OIE) and Food and Agriculture Organization to come together to address the factors responsible for its emergence across the globe.

The emergence and rapid spread of drug-resistant pathogens continue to threaten our ability to treat routine infections which were once treated very effectively. The ineffectiveness of the existing antimicrobials combined with rapid spread of multi- and pan-resistant bacteria is indeed an alarming situation, with an annual 10 million projected deaths by 2050.

Hence, AMR is a major health security issue forcing many countries to adopt regional and national action plans to mitigate the increasing threat of AMR.

AMR occurs naturally over time, usually through genetic changes which is a part of natural evolution. The resistant organisms are found in people, animals, foods, plants and the environment which can spread between and within the sectors.

AMR, particularly antibacterial resistance (ABR) is frequently reported at the interface of human, animal and environment indicating the role of industry, farming, veterinary practices in ABR in addition to human health practices.

The main drivers of AMR include use, misuse and abuse of antimicrobials. The need for antimicrobials arises when basic requirements like clean water, sanitation and hygiene for animals and humans are not met, leading to frequent infection and disease.

Also, the public health infrastructure to prevent the origin and spread of infections in both, the human and veterinary health sector is poor, leading to more frequent use of antimicrobials to treat the diseases.

The Global AMR Surveillance System Report in 2019 revealed that the major clinically relevant antibiotic resistant species are:

- *Acinetobacter* spp.
- *Clostridium difficile*
- *Escherichia coli*
- *Enterococcus* spp.
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Salmonella* spp.
- *Shigella* spp.
- *Streptococcus pneumoniae*
- *Neisseria gonorrhoeae*

These antibiotic resistant species are prevalent both, in humans and animals with exposure to diverse antimicrobials allowed for use in respective sectors.

Quantitatively, the amount of antimicrobials used in animals is comparable to humans but chances of selection of resistant microbes is high in animals due to larger biomass.

Additionally, the practice of using low doses of antimicrobials as growth promoters in food animals provides a suitable environment for emergence of AMR.

There are multiple studies showing an association between repeated exposure to low levels of antimicrobials and emergence of AMR.

Hence, among the drivers of AMR, zoonoses, the diseases which are naturally transmitted between humans and animals, are a major driver that can threaten human health by facilitating the emergence of AMR pathogens. The spread of antibiotic resistance is also determined by geographical and climatic conditions, policies and socioeconomic status.

National level surveillance and monitoring for emergence and spread of AMR is important for evaluating the effectiveness of local, national and global strategies to mitigate AMR.

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## Kerala case study shows how ethnoveterinary practices can curb AMR in livestock

*Ethnoveterinary practices are more cost-effective than allopathic treatment; it also allows farmers to monitor the process*

By KC James

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Livestock production is crucial for the nutritional well-being of people in India. The dairy sector supports the livelihoods of many farmers and contributes to the economy of the country.

India is one of the primary consumers of antibiotics; antimicrobial-resistant (AMR) bacteria are a major public health concern. Antimicrobial-resistant bacteria can be transferred from animals to humans either through direct contact or contaminated food, or indirectly through a contaminated environment.

Antimicrobial resistance causes nearly 700,000 deaths annually across the world. Every country is potentially affected. If not properly addressed, the number could grow to 10 million per year by 2050, making it deadlier than cancer.

AMR occurs when bacteria and other microbes become less susceptible to antibiotics used to treat infections caused by them. The overuse and misuse of antibiotics accelerate the process of antibiotic resistance. Resistant bacteria then spread via healthcare-acquired infections.

It is usually the improper use of antimicrobials in livestock that gathers attention; medicines with a lower dose of active ingredients may also lead to resistance.

Malabar Milk Union, therefore, formulated organised strategies to address the menace. The body ensures broad access to affordable herbal medicines and funds for the development of new treatments covered under ethnoveterinary medicine, besides proper stewardship of existing antimicrobial treatments.

### Strategies framed at Malabar Milk Union to curb AMR

The union collects around eight litres of milk every day from more than 0.1 million farmers. Most farmers rear hybrid cows, whose susceptibility to diseases such as mastitis is high.

The union started work on framing strategies from 2018 onwards. They are elaborated in the table below

Description	Year of operation		
	2018-2019	2019-2020	2020-2021
<b>Goal</b>	Enforcing judicious use of antimicrobials for treating commonly occurring clinical infections in cattle. Advocating ethnoveterinary medicines in replacement of traditional allopathic antimicrobial drugs. Reducing the cost of milk production through limiting the expenses incurred towards using the allopathic antimicrobial drugs.		

	Controlling the antimicrobial residues excreted through milk.		
<b>Modus operandi</b>	The above-mentioned goals are strategically enforced and achieved with the help of village resource persons (VRP). All VRPs are educated about ethnoveterinary medicines and ethnoveterinary practices. Selected interested VRPs are being properly trained at Sabarkantha District Co-operative Milk Producers' Union, Gujarat, on the compounding of ethnoveterinary medicines and implementing ethnoveterinary practices. Installed ethnoveterinary medicines compounding unit at Mananthavady, Wayanad district.		
<b>Number of clinical cases treated through ethnoveterinary practices</b>	Mastitis – 150 cases Diarrhea – 258 cases Pyrexia – 200 cases	Mastitis – 1,916 Diarrhea – 2,202 Pyrexia – 1,634 Immunity boosting bolus - 6,350 cases	Mastitis – 1,271 Diarrhea – 650 Pyrexia – 698 Immunity boosting bolus – 3,628

#### Advantages

- Cost-effective compared to conventional allopathic treatments. A 10-day course of ethnoveterinary medicines for subclinical mastitis treatment costs Rs 200. Conventional allopathic treatment for the same time ranges from Rs 2,000-Rs 4,000.
- The practice ensures zero antimicrobial residual effect in milk.
- Help prevent further severity of clinical infections.
- Farmers prepare and administer the medicines themselves. So they are able to adequately monitor the process.
- Ethnoveterinary practices help reduce the cost of production.

#### Challenges

- Farmers do not completely rely on or trust the practice yet.
- It is time-consuming. Instant effect as exhibited by the conventional allopathic treatments may not be possible here.
- Difficult to practice on animals with acute clinical cases. However, a judicious combination of both allopathic and ethnoveterinary practices may be required for lowering the antimicrobial residual effect in milk.
- The practice can be laborious for farmers since they have to prepare and administer the medicines themselves.

In this current financial year 2021-2022, the application process of appropriate drug license for the manufacturing 10 types of ethnoveterinary medicines — Masticure, Pyrexcare, Immunoboost, Cough Out, Crack Heal, Diar End, Rumotore, Heal All, Milklet and Flyrepel — is under progress in association with the Kerala Ayurvedic Co-operative Society.

The medicines will be distributed across Kerala under the brand name Milma Vet once it obtains the drug license to do so.

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## Nigeria's challenges to implement action plan for food system protection

*Implementing national action plan is cost-intensive and requires human resource*

By Tochi Okwor

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Food animals, fish and vegetables are recognised as significant reservoirs of antibiotic resistant bacteria. The “farm to fork” continuum is an ecosystem where large quantities of antibiotics are used.

Nigeria recognises that antimicrobial resistance (AMR), if left unchecked, has a wide-ranging implication in terms of health security, food security, environmental well-being and socio-economic development of not only Nigeria but globally.

Nigeria keyed into the global AMR agenda by formulating the National Action Plan (NAP) on Antimicrobial Resistance 2017-2022. This foundational NAP attempted to include actions to be taken on human health, food systems and the environment. It sets out to address five focus areas in line with the global NAP.

### **Implementation initiatives**

One of the first steps taken in the implementation of the NAP was the development of Nigeria's AMR governance structure based on the ‘One Health’ approach. A key achievement is the establishment of the national antimicrobial resistance coordination committee (AMRCC).

The purpose of the AMRCC is to guide, oversee and monitor AMR-related activities in all sectors to ensure systematic and comprehensive implementation.

There have been ongoing efforts to create heightened awareness on antibiotic resistance through continuous awareness as well as sensitisation campaigns on hand hygiene and safe food handling practices.

Since 2017, the World Antibiotic Awareness Week has been used by all sectors to create awareness on AMR with various stakeholders in human health, animals and the environment engaged.

Surveillance is an essential step in addressing AMR in the food sector and this can be achieved through an integrated food chain surveillance system from farm to fork. A major achievement in this area in Nigeria is the designation of the National Virology Research Institute as the national reference laboratory for animal health.

The central diagnostic laboratory then coordinates the activities and carries out referral diagnosis for states and private veterinarians.

A robust biosecurity measure in food and agriculture will significantly reduce AMR bacteria from farm to fork. Such a biosecurity effort should use a ‘One Health’ framework and include critical concepts such as good agricultural practices, good hygiene practices, good veterinary practices, hazard analysis and critical control as well as microbiological risk assessment and management.



Actions taken by Nigeria in this area include conducting quarterly meetings of the National Food Safety Management Committee for proper oversight of food safety issues and the development of the farm and transport biosecurity guideline draft, which is currently undergoing stakeholder review.

The National Veterinary Research Institute produces some animal vaccines (bacterial and viral vaccines).

### **Stumbling blocks**

Nigeria's food safety system is regulated by at least three different competent authorities, each with some degree of overlap in responsibilities. There are weaknesses in collaboration and coordination with poor communication among various competent authorities, leading to inefficiencies in resource utilisation and poor levels of control of food safety standards.

The implementation of NAP has been limited in the crop sector and it appears that the current NAP left out key aspects of the crop sector. One challenge of implementing the NAP, particularly in the animal and crop sections, is the cost-intensive nature and human resources needed to achieve the desired impact.

In Nigeria, surveillance programmes for antimicrobial use (AMU) and AMR in animals and plant sectors are either lacking or low. The dearth of data on AMU may be due to the limited coordination with the private sector, livestock keepers and small-scale crop farmers as well as lack of tools and human resources and a weak regulatory framework.

There is no national animal identification and traceability system in place in Nigeria and no registration of livestock owners or livestock premises. This means that livestock management is not regulated.

Concerns have been raised on the use of adulterated feeds in the rearing of the food-producing animals leading to AMR. The provision of veterinary services is done by government and private animal health facilities. However, a majority of these are situated in urban areas with limited provision to the rural areas.

### **Address challenges**

Nigeria has always recognised the need to take a 'One health' approach and developed the NAP in line with this. The weakness observed in various pillars of the response such as environment as well as food and agriculture (non-representation of the crop-producing sector) has further highlighted the need to make more efforts to ensure that line ministries and other stakeholders work together more closely.

We continue to work towards taking ownership of our national AMR response and will continue to make a case for inclusion of AMR activities, including those in the food and animal sector, into the budgets of the line ministries.

The value of good data on AMU and AMR in food animals and crops is very important to support the understanding and management of the AMR problem in the food chain.

Nigeria is working to design targeted surveillance systems for AMU in terrestrial and aquatic animals as well as in the crop production sector.

It is apparent that Nigeria needs to continue improving on its efforts towards utilising the 'One Health' framework and implementing multifaceted and integrated measures to ensure food safety and security, and limit the threat of AMR in the food chain.

Some key challenges have been identified in implementing AMR activities in food systems. Nigeria will use the lessons learnt to develop the next NAP to encompass the human, animal and environmental sectors and address AMR issues all through the "farm to fork" continuum.

*About the author: Tochi Okwor is the chair of Nigeria Antimicrobial Resistance Coordination Committee.*

## What are herbal alternatives for antibiotics in dairy and poultry?

*Enhancing host immunity by using scientifically proven herbs has gained momentum as an alternative to antibiotic growth promoters*

By Anup Kalra and Manoj Saxena  
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Antibiotic resistance has emerged globally as one of the major threats to human health. It leads to an additional burden on the health system as well as treatment failures.

Public health experts agree that overuse, misuse and abuse of antibiotics in intensive animal production for growth promotion contributes significantly to antimicrobial resistance (AMR). Antibiotic growth promoters (AGP) are banned, and there is debate on looking for alternate solutions.

There is a greater knowledge today on the use of herbal alternative growth promoters — phytochemical sources with proven scientific rationale and worldwide acceptance are an example. Due to the increase in demand of antibiotic-free and safe produce, farmers have started to produce antibiotic-free chicken eggs and milk, which fetch higher profits.

Antibiotics are central to modern medicine. They help treat infectious diseases. But bacterial infections are increasingly common, so farmers tend to observe growth promotion with low doses of antibiotics mixed with feed.

More than half of the globally produced antibiotics are used in animals for growth promotion. Finding alternatives for AGPs offers an opportunity out of concern for food safety.

### **Strategies to reduce AMR**

It is imperative to move to alternatives to antibiotic growth promoters to reduce AMR and improve food safety. Many scientific explorations suggest that phytochemical solutions can help grow friendly micro-flora and reduce pathogenic strains, giving proper integrity to the gut walls.

The use of antibiotics as growth promoters can be eliminated without compromising productivity.

Many phytochemical ingredients in nature are known to act against harmful microbes and help in growth promotion without producing resistance. Some examples are Tulsi (basil), Ashwagandha (ginseng) and Amla (gooseberry).

Clinically validated solutions can impart benefits to the farming community. These solutions can be used as feed additives and enhance value of safe animal food production.

Other herbal solutions help:

- Control mastitis
- Improve liver function and health
- Improve skin health
- Improve milk production

- Manage stress in dairy production

Quality and constituents in herbs decide the efficacy and the expected value creation for farmers and stakeholders. Whether the medicinal plant is cultivated in India or abroad makes all the difference. These medicinal plants are produced using certified seeds and quality soil under the supervision of experts.

### **Holistic approach to replace antibiotics**

Antibiotic use for growth promotion, however, can be problematic too. Several herbs reduce the pathogenic load in the intestine, respiratory system as well as other vital organs.

These phytochemicals initiate responses from the natural defence mechanism of the body, so that cytokines acquire the role of natural killer cells and check the microbial population.

This approach to enhance host immunity by using scientifically proven herbs has gained momentum as an alternative to AGPs. This strategy is effective to produce antibiotic-free milk, meat, eggs and other animal proteins.

Solutions made from a mixture of herbs and essential oils have antibacterial (static) and antiviral properties. They also facilitate healing action of gut epithelium. It also has a strong antioxidant property that diminishes the damaging effect of free radicals.

Such solutions have been tested against feed supplements made from Tetracycline, Salinomycin, Enramycin, Bacitracin Methyl Salicylate, Roxarsone and many other popular alternative growth promoters with great success.

The powerful synergistic combination of herbal extracts and essential oils products adsorbs and inactivates enterotoxins, and has antibacterial and antiviral activities. It protects the gastro-intestinal mucosa and maintains a healthy gut.

They also exhibit inhibitory effects on *Clostridium*, *Salmonella*, *E.coli*. They also help increase helpful bacteria like lactobacillus and bifidobacteriam.

They also provide a reprieve from respiratory distress. Ingredients herbs and essential oils not only have antiviral and antibacterial effects, but also help build immunity locally. Robust action of cilia and mucus-producing defence mechanism helps animal / birds fight respiratory infection without lowering productivity.

We need to look at the responsible use of antibiotics, especially the ones used for growth promotion. Our efforts simultaneously should focus on nutrition, health and hygiene index to keep animals healthy and productive.

It is time we create consumer awareness to mitigate the risk of AMR under the National Action Plan on AMR.

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## How resistance to antibiotics develops

*Antimicrobials from food-producing animals enter the environment through excreta or animal manure*

By Ajay Kumar Upadhyay and Ram Swaroop Chauhan  
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Antimicrobial Awareness Week 2021: Resistance from animals and environmental routes

Resistance is the ability of a bacterium to work against the antagonising effect of an antimicrobial agent, upon reproduction prevention or microbicidal (an agent that destroys microbes).



The development of resistance to antimicrobial agents in microbes often develops as a result of unnecessary and inappropriate use of antimicrobials.

Today, while the world is trying to develop new drugs, there are difficulties in treatment as a result of rapid development of resistance to these drugs.

The development of resistance to antimicrobial is a major public health problem all over the world.

### **The four types of resistance:**

#### **I. Natural (intrinsic, structural) resistance**

This kind of resistance is caused by the structural characteristics of microbes and it is not associated with the use of antimicrobials. It has no hereditary property.

It develops as a result of the natural resistance, or the microorganisms not including the structure of the target antimicrobial, or antimicrobial not reaching its target due to its characteristics.

Gram negative bacteria vancomycin, for instance, does not pass in the outer membrane. So, gram-negative bacteria is naturally resistant to vancomycin.

Similarly, L-form shape of bacteria which are cell wall-deficient forms of the bacteria, and the bacteria such as cell wall-less cell Mycoplasma and Ureaplasma are naturally resistant to beta-lactam antibiotics that inhibit the cell wall synthesis.

#### **II. Acquired resistance**

As result of the changes in the genetic characteristics of microbes, an acquired resistance occurs because it is not being affected by the antimicrobial it has been responsive to before.

This kind of resistance occurs mainly due to structures of chromosomes or extra chromosomals such as plasmid, transposon and others.

#### **III. Cross resistance**

Some microorganisms are resistant to a certain drug that acts with the same or similar mechanism as some other drugs.

This resistance is usually observed against antibiotics whose structures are similar — resistance between erythromycin, neomycin-kanamycin or resistance between cephalosporins and penicillin.

However, sometimes it can also be seen in completely unrelated drug groups. There is an example of cross-resistance between erythromycin-lincomycin. This may be chromosomal or extra-chromosomal origin.

#### **IV. Multi-drug resistance and pan-resistance**

Multidrug-resistant organisms are usually bacteria that have become resistant to the antibiotics used to treat them. This means that a particular drug is no longer able to kill or control the bacteria.

Inappropriate use of antibiotics for therapy resulted in the selection of pathogenic bacteria resistant to multiple drugs. Multidrug resistance in bacteria can occur by either of the following mechanisms:

These bacteria may accumulate multiple genes, each coding for resistance to a single drug. This type of resistance occurs typically on resistance plasmids.

Resistance may also occur by the increased expression of genes that code for multidrug efflux pumps, enzymatic inactivation, changes in the structure of the target, among others.

#### **Mechanism of resistance of antimicrobial**

- **Change in the target site:** The changes that occur in the receptor connected to the drug and the region of the connection 'Connection of the antibiotics' target areas are different. They can be various enzymes and ribosomes. Resistance associated with alterations in the ribosomal target are the most frequently observed in macrolide antibiotics. Mutations in penicillin-binding proteins (beta-lactamase enzymes) and *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Enterococcus faecium* strains can develop resistance to penicillin.
- **Enzymatic inactivation of antibiotics:** Most gram-positive and gram-negative bacteria synthesise enzymes that degrade antibiotics. This enzymatic inactivation mechanism is one of the most important mechanisms of resistance. In this group, beta-lactamases, aminoglycosides, modifying enzymes (acetylase, fosforiase adenilaz and enzymes) degrade beta-lactam antibiotics and continually increase their number of which inactivates enzymes, include chloramphenicol and erythromycin.
- **Reduction of the inner and outer membrane permeability:** This resistance is due to changes in the internal and external membrane permeability, decrease in drug uptake into the cell or quick ejection from the active resistance of the pump systems. As a result of a change in membrane permeability, decreased porin mutations in resistant strains can occur in proteins.
- **Flush out of the drug (active pump system):** Resistance developing through the active pump systems is mostly common in the tetracycline group of antibiotics. Tetracyclines are thrown out with an energy-dependent active pumping system and cannot accumulate in the cell. Such resistance is in control of the plasmid and chromosomal. Active pumping systems are effective in resisting quinolones, 14-membered macrolides, streptogramins, chloramphenicol and beta-lactams.
- **Using an alternative metabolic pathway:** Unlike some of the changes in the target in bacteria, a new pathway for drug-susceptibility eliminates the need to develop an objective.

Bacteria can gain the property of getting ready folate from the environment instead of synthesising folate.

### **Antibiotic resistance dissemination**

Antimicrobial dissemination from food-producing animals to the surrounding environment takes place through either the excretion of antimicrobials through urine or faeces into surface waters and soils, or the application of animal manure as fertiliser to soil or ponds.

Untreated animal waste is used for a variety of purposes in subsistence economies. Intestines from poultry are also used as feed for aquaculture, leading to higher levels of resistance in *Enterococcus* spp. isolates in fish intestines.

Antibiotics are extensively used both on human and animal health practices in developed and developing countries of the world, mainly for treatment and control of various diseases.

However, the use, misuse and overuse of these medicines contributed to favourable conditions for the emergence, occurrence and development of antibiotic resistant bacteria.

Views expressed are the author's own and don't necessarily reflect those of Down To Earth.

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## How the environment plays a role in AMR

*The environment is key to the One Health approach to address AMR, which is being strongly advocated by the United Nations and other actors*

By Divya Datt and Rajesh Bhatia  
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Antimicrobial resistance (AMR) is the inability of the antimicrobial agent (commonly an antibiotic) to treat a person or animal suffering from infectious diseases when administered in standard doses. It has become one of the greatest challenges in the efforts to fight infectious diseases.

The well-documented public health impact of this phenomenon is immense.

The failure to halt or reverse this trend is likely to push the world into a post-antibiotic era where even small injuries may become difficult to treat and major developments in complex and life-saving technologies may get negated. In a low estimate, already, 700,000 people die each year of resistant infections.

The key factors contributing to AMR are misuse and overuse of antibiotics in human health, food-animal production and agriculture, along with poor management of waste emanating from households, farms, factories and human and veterinary healthcare facilities.

The emergence of resistance in microbes at a genetic level is an inevitable biological phenomenon. But their interaction with varying doses of antimicrobials under a conducive milieu accelerates the selection of resistant sub-populations.

Most of this interaction takes place in the environment, especially in medical and municipal waste, sewage, effluents from industry, farms, aquafarming and health facilities.

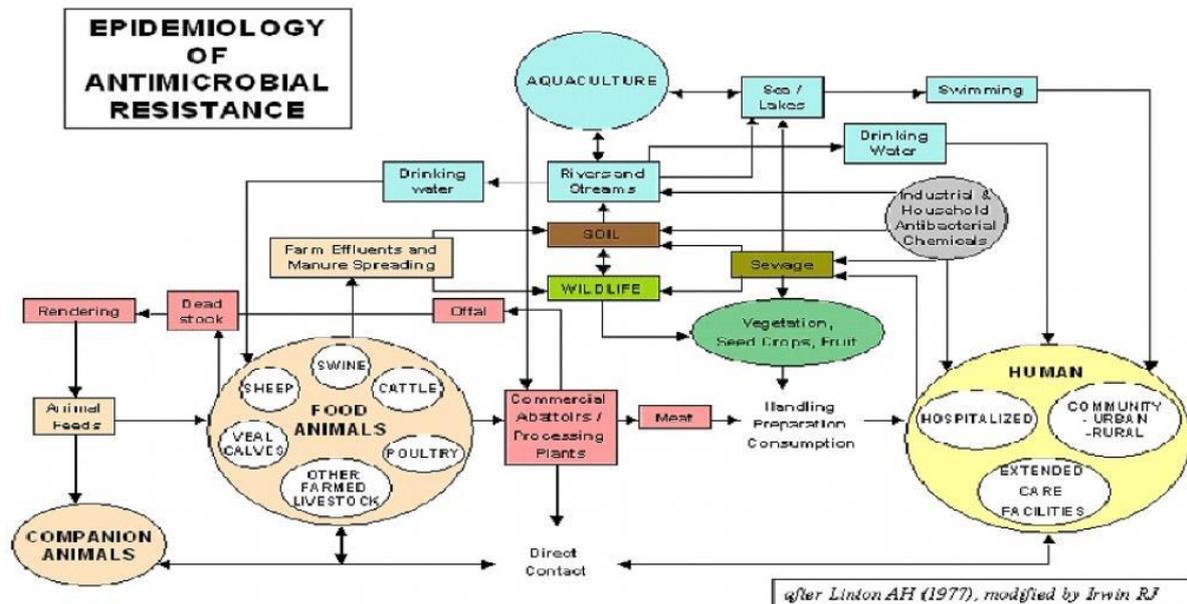
There is strong evidence that the release of antimicrobial compounds to the environment, combined with direct contact between natural bacterial communities and discharged resistant bacteria, are driving microbial evolution and the emergence of more resistant strains.

The United Nations Environment Programme (UNEP) identified AMR as one of six emerging issues of environmental concern in its FRONTIERS Report in 2017.

The environment is key to the One Health approach to address AMR, which is being strongly advocated by the United Nations and other actors.

Unfortunately, the environmental sector has not yet been accorded priority in most developing countries and national efforts against AMR have been mainly implemented through human and animal health sectors and restricted to their respective domains.

UNEP has been working closely with the Tripartite organisations — the Food and Agriculture



Organization (FAO), the World Organization for Animal Health (OIE) and the World Health Organization (WHO) — to strengthen environmental aspects in addressing AMR within the One Health approach.

Source: Adapted from Antimicrobial Resistance Surveillance in Canada by R Irwin (2011)

In 2017, a resolution was passed for the UNEP to prepare, in partnership with WHO, OIE, FAO and other organizations, a report on the environmental impacts of AMR and the causes for the development and spread of resistance in the environment.

The “environmental dimensions of antimicrobial resistance” report will be released at the next UN Environment Assembly in February 2022.

In India, UNEP is working with the National Institute for Cholera and Enteric Diseases, which is the Antimicrobial Resistance Hub of the Indian Council of Medical Research.

It is working to collate and analyse the existing science on environmental contamination from antimicrobial waste from households and hospitals and livestock, poultry, aquaculture and pharmaceutical manufacturing facilities.

The UNEP is getting funding support for the India project from the Government of Norway.

This report is expected to be ready by January 2022 and shall be a resource in revision of the National Action Plan on AMR for 2022-2025.

The UNEP is supporting this project under the larger framework of Environment and Health, being led by the Inter-Ministerial Steering Group on Environment and Health in India, co-chaired by the Ministry of Health and Family Welfare and the Ministry of Environment, Forest and Climate Change.

AMR is nothing less than a silent pandemic. Even as we advance the science on its different drivers, we must come together quickly to act based on what science is already telling us.

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## Why water is important in the AMR debate

*Access to safe water is one of the prerequisites for maintaining sound health and environment in a community and is also a responsibility of administrative stakeholders*

By Ashok J Tamhankar and Vishal Diwan  
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Antibiotics are one of the most common medicines for humans and animals. A large amount of antibiotics get released into wastewater due to excretion from humans and animals and the disposal of unused compounds from domestic as well as healthcare systems like hospitals.

Another large source is the pharmaceutical industries, which contribute to the spread of antibiotics in the environment through their effluents.

A large proportion of antibiotics are also used in animals for purposes other than treatment of disease such as as growth promoters, which also end up in aquatic systems through surface flow from animal and fish / prawn / shrimp farms (aquaculture).

Any exposure to antimicrobials by microbes starts the process of development of antimicrobial resistance in microbes, that influences quick recovery from infectious diseases of humans and animals.

Globally, two million tonnes of sewage, industrial and agricultural waste is discharged into the world's waterways. It is estimated that more than 80 per cent of Asia's wastewater is discharged untreated, polluting both groundwater and surface water sources, where they pollute the usable water supply.

Antibiotic residues and resistant bacteria have been detected in various aquatic compartments of environments such as rivers, ponds, lakes in India, as well as globally.

For example, samples from the Ganga at Haridwar and Rishikesh have shown the presence of antibiotics like fluoroquinolones, sulphonamides, erythromycin and tetracycline in amounts of over 100 nanogram per litre (ng/litre).

Groundwater at Patna was found to contain Sulpha up to 360 ng/litre. Samples of bacteria from the Yamuna have shown a high level of resistance against tetracycline and polymyxin B.

Bacteria from samples of drinking water from Lucknow have been found resistant to antibiotics. Water samples from the Kshipra river at Ujjain have exhibited the presence of antibiotics and a high degree of resistance in the bacteria therein.

Hospital wastewater in Ujjain was found to contain antibiotics upto 600 microgram per litre (mg / litre). Effluents from drug manufactures near Pantacheru near Hyderabad have been found to contain antibiotics upto 31 mg / litre.

Other countries are no exception and surface water or ground water from China, the United States, Serbia, Italy, Bangladesh and Malaysia have also been found to contain antibiotics.

Bacterial samples from wastewater irrigated soil have a significantly higher antimicrobial resistance profile when compared to those irrigated with unpolluted groundwater.

Fish and other species, breeding in water that contain antimicrobials and resistant bacteria, are harvested for food purposes, thus facilitating the entry of resistant bacteria and antimicrobials in the food chain.

Antimicrobials have been detected in wild fish in many countries including in fishes from rivers in China and India, seawater from Poland, etc and they are known to affect the endocrine system.

For example, sulphonamides influence thyroid endocrine disruption and alteration of concentration of T4 and Plasma E2; Tetracyclines influence the steroidogenesis pathway, Thyroid endocrine disruption, T3 concentrations, T3/T4 ratio, Whole body TSH and alteration of gene expression level in HPT.

Erythromycin influences energy metabolism, gene-related oxidative phosphorylation, lipid metabolism and neuroendocrine disruption. The trophic transfer through the foodchain can very easily result in them influencing human and animal systems.

India is an important player in global aquaculture production and its aquaculture industry is an important contributor to India's food security. To ensure sufficient production in the aquaculture set up, large quantities of antibiotics are used in fish / prawn / shrimp cultivation.

This is potentially dangerous for human health and there is a lot of concern about this all over the world, as this may result in water and sediment contamination and the development of antibiotic resistance genes.

In integrated poultry-fish farming, the use of antibiotics in poultry feed can cause the prevalence of antibiotic-resistant bacteria in pond environments and its consequent spread can be a matter of great concern.

Access to safe water is one of the prerequisites for maintaining sound health and environment in a community and is also a responsibility of administrative stakeholders.

FAO has developed a Code of Conduct for aquaculture and fisheries. The guidelines inform that antibiotics need to be preferably used under veterinary supervision and preventive use of antibiotics in aquaculture must be avoided as far as possible.

It has been stated that states should regulate the use of chemicals in aquaculture that are hazardous to human and animal health and the environment and that marketing and the use of drugs that have not been certified for aquatic use should be strictly regulated.

It is also important to advise consumers on the proper storage and disposal of unwanted antimicrobials. Consumers can then serve as environmental stewards to reduce water pollution.

It will be a good initiative to standardise and implement antimicrobial take-back programmes. It is also essential to formulate rules and regulations regarding waste water treatment for antibiotics removal to avoid entry of antibiotics into the environment.

Relevant governmental administrative units, scientific communities, civil societies, non-profits, etc need to work in tandem to advise all relevant stakeholders such as concerned ministries, pharmaceutical industry, aquaculture industry, municipalities, consumers, etc. on the proper use, storage and disposal of antimicrobials.

The joint initiative can then serve as environmental stewards to reduce pollution of aquatic environment by antimicrobials and consequently also of resistant pathogens and thus help reduction in antimicrobial resistance.

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## Zimbabwe's initiatives to prevent and contain AMR

*A look at the steps taken by the Government of Zimbabwe to contain AMR in the country*

By Sylvia Yomisi

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The Ministry of Environment, Climate, Tourism and Hospitality Industry in Zimbabwe is committed to the containment of antimicrobial resistance (AMR) in the environment.



This commitment was shown by the signing of the National Action Plan (NAP) by the then minister of the Ministry of Environment, Climate, Tourism and Hospitality Industries, Oppah Muchinguri in 2017, which is further supported by the current minister.

### **Key activities**

#### **AMR Surveillance**

One of the key pillars of the NAP is surveillance. The environment sector, through the Environmental Management Agency (EMA) is actively involved in the surveillance of antimicrobial resistance in the environment.

So far, 32 surveillance points have been established in two major cities, that is Harare and Bulawayo. At the moment, the Agency can only track resistance in the environment.

However, it is unable to determine residual antibiotics as this requires an LC-MS-MS which the Environmental Management Agency Laboratory (EMAL), does not have.

#### **AGISAR project**

The EMAL took part in the WHO Advisory Group on Integrated Antimicrobial Resistance (AGISAR). A total of 119 samples were analysed under this project.

#### **Tricycle Project**

Currently, EMAL is involved in the tricycle project which is tracking ESBL (*E.coli*) in the environment, animal and human sectors. So far, eight sampling points have been established in Harare and Marondera. A total of 40 samples have been collected so far and analysis is still underway.

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