

ANTIBIOTICS IN AGRICULTURE: A POTENTIAL SOURCE OF ANTIMICROBIAL RESISTANCE



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INTRODUCTION

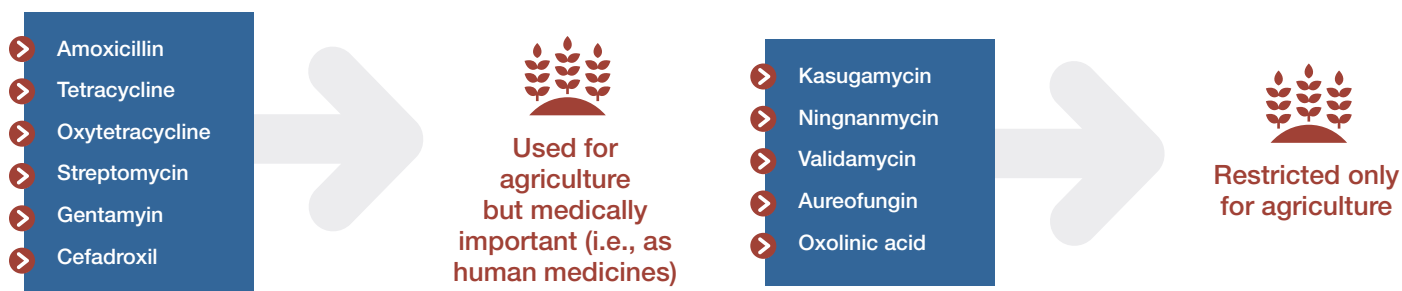
Antibiotics are extensively used in agriculture to prevent and cure various diseases in crops, besides their major applications in humans and animals. **Antimicrobials such as antibiotics and fungicides are not only applied to agricultural crops but also used in the agro-based industries, for example, for the production of biofuel by-products.**¹ The tripartite of Food and Agricultural Organization of the United Nations (FAO), World Health Organization (WHO) and World Organization for Animal Health (OIE) have recognized the use of antibiotics in agriculture as an emerging area of concern mainly because of the apprehension that antibiotic resistance to medically important antibiotics might be transferred to human pathogens.

ANTIBIOTIC CONSUMPTION FOR CROPS

Taylor and Reeder² in 2020 revealed the use of 11 antibiotics (as given below) belonging to 8 classes being used for crops globally. The study further indicated that there were variations in the amount of antibiotics being recommended based on:

- Different regions of the world
- Type of antibiotic
- Crop to which they were applied and
- Diseases they were being recommended against

The major antibiotics used for crops and their applications are provided in Annexure I.



Streptomycin is the most commonly used antibiotic in plant agriculture to treat diseases such as fire blight since the early 1940s.

SOME OF THE KEY FACTS REGARDING THE ANTIBIOTICS USAGE IN CROPS:

- Globally, the most frequently used antibiotic is **streptomycin** followed by, **tetracycline** and **kasugamycin**³
- Antibiotics such as, streptomycin, kasugamycin, aureofungin, ningnanmycin, oxolinic acid, and validamycin have also been used against other pathogen groups including fungi⁴, water moulds⁵ and viruses⁶.
- Global data showed that antibiotics are being applied on over 100 crops, with rice being the most common crop to receive antibiotics. Tomato and citrus crops were the other crops on which antibiotics were frequently applied.
- As per existing data, USA is the biggest user of antibiotics in plant agriculture (approximately 70,000 kg per annum).

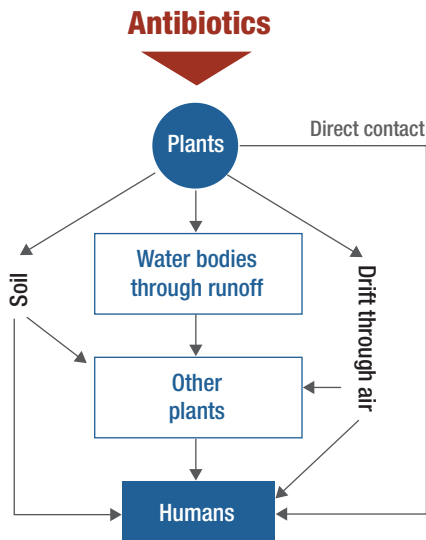


Antibiotics used for crop protection are typically formulated as powders containing the particular antibiotic as an active ingredient. The powder is dissolved or suspended in water to obtain recommended antibiotic concentrations and then sprayed as a fine mist onto the susceptible part of the plant.³

ANTIBIOTIC USE FOR CROPS: ISSUES AND CONCERNS

- Antibiotics are recommended as a preventive measure against bacterial diseases and are used even in the absence of disease symptoms
- Indiscriminate use of antibiotics at rates more than the recommended dosages
- Antibiotics even used for crops and diseases other than the recommended ones
- Although antibiotics have no activity against arthropods, they are recommended against insects and mites²
- Presence of residual antibiotics in the environment after spraying on crops and their linkages to antimicrobial resistance (AMR) remains a matter of concern
- Antimicrobials may persist on plants, resulting in food safety risks associated with toxicological, immunological, or allergic reactions⁷
- **Antibiotics are used against target species; however, there is significant evidence that antibiotics adversely affect the growth and performance of plants such as alteration in biomass production, toxic effects on roots, etc.**⁸

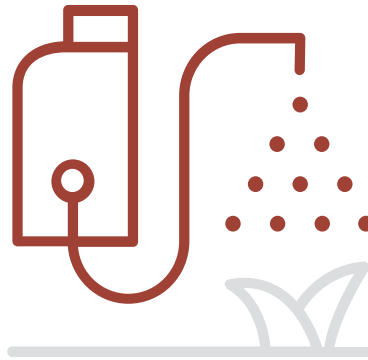
POTENTIAL RISK OF ANTIMICROBIAL RESISTANCE



The crucial antibiotics such as streptomycin and tetracycline are commonly used in high doses on crops, which can contribute to the AMR crisis as the antibiotic-resistant genes may spread to medically important bacteria.

- Streptomycin: Primarily used for treating moderate to severe tuberculosis in humans, also used to treat pneumonia, influenza and other infections caused by certain bacteria
 - AMR evolution in streptomycin-treated apple orchards has been observed in the US in plant pathogens, epiphytic bacteria, and even an opportunistic human pathogen³
 - Streptomycin resistance is relatively widespread among plant-pathogenic bacteria because of its longest use over a large geographic region and for treatment of a large number of crops⁹
- Tetracycline: Used to treat infections caused by bacteria including pneumonia and other respiratory tract infections, certain infections of skin, eye, lymphatic, intestinal, genital and urinary systems
 - Tetracycline resistance has been reported in a few plant-pathogenic bacteria such as *P. syringae* and *Agrobacterium tumefaciens*⁹

Antibiotic use in crops provides a potential route for the spread of antibiotic resistance. There is a major concern over their agricultural use because there is a possibility of the resistance to spread to medically important bacteria.



Antibiotics are often mixed with other agrochemicals and used for crops, which has led to concerns over interactions that might promote cross-resistance or co-selection for antibiotic resistance. Studies have shown that when antibiotics are mixed with other agrochemicals, bacteria can develop resistance to the antibiotic up to 100,000 times faster.²

IMPACT OF AMR ON AGRICULTURE

- Antibiotic use can lead to the emergence and transmission of resistant genes and resistant bacteria between plant species
- AMR can lead to production losses, damage livelihoods and endanger food security

ANTIBIOTICS IN AGRICULTURE: GLOBAL APPROACH TO COMBAT AMR

The issue of antibiotics in agricultural and animal use was raised for the first time by the tripartite alliance involving WHO, OIE, and FAO formed in 2003 under the “One Health” approach to combat AMR globally. This led to the categorization of medicines into critically important, highly important, and important drugs for human health to guide their use for animals and crops.

The WHO action plan on AMR adopted in 2015 also focuses on antibiotic use in agriculture. The Objective 4 of the WHO action plan emphasizes on regulating the use of antimicrobial agents in agriculture, while the Objective 1 focuses on undertaking research to identify alternatives to nontherapeutic uses of antimicrobial agents in agriculture.

Centre for Agriculture and Bioscience International (CABI) (www.cabi.org) Plantwise (www.plantwise.org) is an agricultural development programme providing support and training to plant-based agricultural extension services in 33 countries in Africa, Asia and the Americas. The data collected based on examination of the plant sample and dialogue with the farmer is uploaded into the international database known as the Online Management System (POMS). The POMS database is an important resource in assessing the level of antibiotic use in countries.

At present, the European Union does not approve any antibiotic as active ingredients in pesticides.² In the UK, antibiotics, including streptomycin and oxytetracycline, have been used in the past on ornamental plants but currently, there are no antibiotics authorised for plant use.

Streptomycin use is approved in the US, Canada, Israel, New Zealand, Mexico, some Central and Latin American nations and Southeast Asia. As of June 2016, the Chinese certificate for streptomycin use in agricultural production expired and has not been renewed.⁷

Brazil has banned medically critical antibiotics (streptomycin and oxytetracycline) for use on crops.

Kasugamycin is approved for use in Brazil, USA and China.¹⁰

INDIA'S REGULATION ON ANTIBIOTICS USE IN AGRICULTURE

Antibiotics used for agricultural crops in India are registered as pesticides (fungicides) under Section 9 of the Insecticide Act, 1968 by the Central Insecticide Board and Registration Committee (CIB&RC), Directorate of Plant Protection Quarantine & Storage, Ministry of Agriculture & Farmers Welfare, Government of India.



In India, antibiotics use for human and animal health are regulated by the Central Drugs Standard Control Organisation (CDSCO) under the Drugs and Cosmetic Act 1940 and Rules 1945. However, the antibiotics used on crops do not fall within the purview of the definition of drug as stated in the Drugs and Cosmetic Act 1940. Therefore, CDSCO does not have any role in regulating antibiotics use on crops. Moreover, the State drug authority cannot exercise any control over companies that manufacture or sell antibiotics for use in crops as these products are registered and sold as pesticides.

Streptomycin, i.e., a 90:10 mix of streptomycin and tetracycline is recommended for use on 8 crops in India.ⁱ

Antimicrobials	Crops	Common name of the disease
Streptomycin + Tetracycline	Apple	Fire blight
	Beans	Halo blight
	Citrus	Citrus canker
	Potato	Bacterial soft rot and backleg
	Tobacco	Wildfire
	Tomato	Bacterial Leaf spot
	Rice (Paddy)	Bacterial Leaf blight
	Tea	Blister Blight
Kasugamycin	Rice (Paddy)	Blast
	Tomato	Early blight
Kasugamycin + copper oxychloride	Grapes	Anthracnose, Bacterial leaf spot
	Rice (Paddy)	Leaf blast, Neck blast
	Pomegranate	Bacterial blight, leaf spot, Fruit rot and Anthracnose
Validamycin	Rice (Paddy)	Sheath Blight
Validamycin + Hexaconazole	Rice (Paddy)	Blast & Sheath blight
Aureofungin	Rice (Paddy)	Blast, Brown leaf spot
	Grapes	Downy mildew Anthracnose
	Citrus	Gummosis
	Apple	Powdery mildew White root rot
	Potato	Early blight

The National Action Plan on Antimicrobial Resistance (NAP-AMR) 2017-21 of India laid emphasis on optimizing the use of antimicrobials in agriculture through strengthening regulations, ensuring access and surveillance of antimicrobial use, and antimicrobial stewardship in agriculture.ⁱⁱ It called upon States and Union territories to develop their own plans.

Major interventions and activities in NAP-AMR concerning agriculture include:

- Strengthen and consolidate AMR and related topics as core components of professional education and training
 - Review/revise curricula of professionals in agriculture
 - Develop training resources (including online courses) on antibiotic resistance and use for capacity development among agricultural professionals
 - Implement trainings on AMR for all key stakeholders such as food and agriculture scientists
 - Institutionalise national surveillance system for antimicrobial use (AMU) in agriculture and food sectors
 - Standardise tools to measure consumption of antibiotics in food and agriculture
- Establish antimicrobial stewardship programmes for rational use of antimicrobials in agriculture and food processing units
- Establish and implement national policies on use of antimicrobial agents in agriculture
 - Implement and monitor national plan to restrict use of critically important antibiotics in agriculture

ⁱ http://ppqs.gov.in/sites/default/files/major_use_of_pesticide_fungicide_as_on_30.11.2021.pdf

ⁱⁱ <https://ncdc.gov.in/WriteReadData/linkimages/AMR/File645.pdf>

The Food Safety and Standards Authority of India (FSSAI) has specific MRL for the antibioticsⁱⁱⁱ

- MRL for insecticides (including some antibiotics registered as insecticides) in foods

Name of the antimicrobial	Food	Maximum Residue Limit (MRL) in mg/kg
Kasugamycin	Rice	0.05
	Tomato	0.05
Validamycin	Rice	0.01

On December 17, 2021, the Union Ministry of Agriculture and Farmers Welfare, notified the order^{iv} on ‘Prohibition of Streptomycin + Tetracycline in agriculture’, which prohibits import, manufacture or formulation of Streptomycin and Tetracycline for use in agriculture from February 1, 2022. The order ensures a complete ban on the use of the two antibiotics in agriculture January 1, 2024, onwards.

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iii https://www.fssai.gov.in/upload/uploadfiles/files/Compendium_Contaminants_Regulations_20_08_2020.pdf

iv <https://egazette.nic.in/WriteReadData/2021/231955.pdf>

ANNEXURE I: ANTIBIOTICS USED FOR CROPS AND THEIR APPLICATIONS

Antibiotics	Applications
Kasugamycin	<ul style="list-style-type: none"> ✓ Isolated from <i>Streptomyces kasugaensis</i> and exhibits antibiotic and fungicidal properties ✓ Originally developed for use in rice with action against the fungal disease, rice blast (<i>Mangnaporthae oryzae</i>)
Aureofungin	<ul style="list-style-type: none"> ✓ A heptaene antibiotic extracted from <i>Streptomyces cinnamoseous</i> var. <i>terricola</i>. ✓ A broad-spectrum systemic fungicide, effective against a wide variety of fungi
Validamycin	<ul style="list-style-type: none"> ✓ An antifungal antibiotic produced by <i>Streptomyces hygrosopicus</i> var. <i>limoneus</i> ✓ Used to control sheath-blight disease in rice and is most effective against soil-borne pathogens
Oxolinic acid	<ul style="list-style-type: none"> ✓ It had been used in human medicine in several countries in the past. However, its use in human medicine has largely been replaced by the fluoroquinolone antibiotics ✓ Reported to be effective against <i>Burkholderia glumae</i>, bacteria causing grain rot, sheath rot, seedling rot, and bacterial panicle blight
Streptomycin	<ul style="list-style-type: none"> ✓ An aminoglycoside antibiotic produced by <i>Streptomyces griseus</i> with activity against both gram-negative and gram-positive bacteria ✓ Primary uses on apple, pear, and related ornamental trees for the control of fire blight caused by <i>Erwinia amylovora</i>
Oxytetracycline	<ul style="list-style-type: none"> ✓ Naturally produced tetracycline antibiotic predominantly used to control fireblight in apple and pears ✓ Used on an emergency basis on apple in specific regions where streptomycin-resistant strains of <i>E. amylovora</i> have been documented

ANNEXURE II: SOURCE OF IMPORT/INDIGENOUS MANUFACTURERS OF ANTIBIOTICS USED FOR CROPS IN INDIA^v

Antibiotics	Indigenous manufacturer	Approved Source of Import
Streptomycin + Tetracycline	Hindustan Antibiotics Ltd, Pune	
Kasugamycin Technical 64% min		Hokko Chemical Industry Co. Ltd., Tokyo, Japan (through Arysta Life Science, Corporation, Tokyo)
Validamycin Technical 64% min.		<ul style="list-style-type: none">Sumitomo Chemical Takeda AgroCo. Ltd., Japan (through Arysta Life Science Corporation, Japan)Sumitomo Chemical Co. Ltd., Singapore (through Sumitomo Chemical Singapore Pte. Ltd., Singapore)Sumitomo Chemical Co. Ltd., Tokyo, Japan (through Summit Agro International Co. Ltd., Tokyo, Japan)Zhejiang Tonglu Huifeng Biochemical Co. Ltd., Zhejiang, China (through Willowood Agro Chem Ltd. Hong Kong)

^v http://ppqs.gov.in/sites/default/files/source_of_import_and_list_of_indigenous_manufacturers_of_insecticides_as_on_30.11.2020.pdf

For more information, please contact:

Toxics Link

E-224, 1st Floor,
East of Kailash

New Delhi – 110065

E: info@toxicslink.org

Supervised by

Piyush Mohapatra; piyush@toxicslink.org

Research and Compiled by

Dr. Omkar Gaonkar, omkar@toxicslink.org