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Review

Antimicrobial Use and Resistance in Plant Agriculture: A One Health Perspective

Sally A. Miller [1,2], Jorge Pinto Ferreira [3] and Jeffrey T. LeJeune [3,*,†]

[1] Department of Plant Pathology, The Ohio State University, Wooster, OH 44691, USA; miller.769@osu.edu
[2] Infectious Diseases Institute, a FAO Reference Centre for Antimicrobial Resistance, The Ohio State University, Columbus, OH 43210, USA
[3] Food and Agriculture Organization of the United Nations (FAO), 00153 Rome, Italy; Jorge.PintoFerreira@fao.org
* Correspondence: Jeffrey.Lejeune@fao.org

Abstract: Bactericides, fungicides, and other pesticides play an important role in the management of plant diseases. However, their use can result in residues on plants and in the environment, with potentially detrimental consequences. The use of streptomycin, oxytetracycline, copper-based products, and some fungicides is correlated with increased resistance among plant pathogens to these agents. Likewise, the recent rise in the incidence of environmental triazole fungicide-resistant *Aspergillus fumigatus*, the cause of aspergillosis in humans, has caused concern, particularly in Europe. Through horizontal gene transfer, genes can be exchanged among a variety of bacteria in the plant production environment, including phytopathogens, soil bacteria, and zoonotic bacteria that are occasionally present in that environment and in the food chain. Through mechanisms of horizontal gene transfer, co-resistance, cross-resistance, and gene up-regulation, resistance to one compound may confer resistance and multi-drug resistance to other similar, or even very dissimilar, compounds. Given the global rise in antimicrobial-resistant (AMR) organisms, and their effects on plant, animal, and human health, the prudent use of pesticides is required to maintain their effectiveness for food security and sustainable production, and to minimize the emergence and transmission of AMR organisms from horticultural sources.

Keywords: agriculture; horticulture; antimicrobial resistance (AMR); antimicrobial use (AMU); plants; crops; One Health

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1. The Problem of Antimicrobial Resistance (AMR)

Since the application of pesticides to plants and plant products exerts selective pressure on both target and non-target species, one must consider all the impacts of pesticide use on all the components of the plant production environment—direct and indirect, intended and unintended. There are therefore two different resistances to be considered:

1. Resistance in plant pathogens to pesticides upon repeated exposure, which may be avoided by utilizing different management approaches.
2. Resistance in human and animal microorganisms evolved through pesticide use.

In the United States alone, crop losses directly due to pesticide resistance are estimated to be approximately 1.5 billion USD per year [1]. The potential direct toxic effects of pesticide application on humans and non-target terrestrial and aquatic species, as well as environmental contamination, are typically assessed prior to approval. However, the impact of plant production chemicals on the ecology of the phytobiome, and particularly on antimicrobial resistance development in zoonotic, saprophytic, and resident plant and soil microorganisms, has received less attention [2]. Specifically, the problem of antimicrobial

resistance is further exacerbated because of similarities in resistance mechanisms and genetic linkages. The use of one pesticide may select for the emergence of multiple resistance phenotypes within a single organism [3,4]. Finally, some products may be applied to plants without any intent or expectation of effects on microbial communities, but may nevertheless influence the microbial components of the phytobiome in unexpected ways.

The use of pesticides is paradoxically associated with a loss in their effectiveness. Resistance to specific active substances has required the retirement of certain pesticides, prompted the search for new more effective products, and initiated a movement towards more integrated pest management (IPM) approaches for pest and disease control [5]. The problem of resistance and selection is exacerbated by the potential of co-selection and cross-resistance. Co-selection is a result of genetic linkages between genes responsible for resistance. In this scenario, multiple different genes responsible for separate resistance phenotypes are unique, but because of their physical proximity to one another on DNA, they are transmitted in tandem. Thus, environmental stress that selects for one gene automatically carries with it the co-selection of the second gene. This is common in instances in which resistance genes are encoded on multi-drug resistance plasmids; selection for one gene results in the maintenance of the entire plasmid that encodes resistance to multiple drugs. Cross-resistance occurs when the genetic elements conferring resistance to multiple antimicrobial agents are common among microorganisms, and a single molecular mechanism is responsible for resistance to multiple agents. For example, efflux pumps in bacteria can confer resistance to many different classes of antibiotics and also to disinfectants and metals (see below).

Although the development of antimicrobial resistance is a natural process, the widespread and sometimes indiscriminate use of antimicrobials in medicine, agriculture, and industry has accelerated the process and propelled the emergence and spread of antimicrobial resistance, one of the world's most pressing public health problems. Currently, infections by AMR pathogens cause over 700,000 deaths annually. If left uncontrolled, by 2050 it is estimated that AMR infections will be responsible, globally, for 10 million deaths each year, and a cumulative cost of at least 100 trillion USD to the world's economy [6]. The drivers and dynamics of antimicrobial resistance emergence and dissemination are complex [7], and the attributable contribution of specific actors and uses (medical, veterinary, agricultural) of antimicrobials to the problem of AMR is uncertain and controversial.

In light of heightened global concern regarding antimicrobial resistance, all 193 member states of the UN General Assembly passed a resolution in September 2016 to develop multi-sectoral, One Health, national action plans to tackle the problem [8]. Agricultural systems play key roles in the emergence of antimicrobial resistance and in its prevention. This includes compliance with voluntary appropriate use guidelines, and the establishment, strengthening, and enforcement of, and compliance with, regulatory frameworks to better monitor and control the use of antimicrobials, and curb the rate of resistance development in agriculture. A review of the evidence concerning the association between the use of antimicrobials on crops and AMR microbes in foods and the environment fills a critical initial step in developing science-based risk management guidelines, standards, and advice for control.

2. Mechanisms of Resistance

The development of resistance is a natural process that is observed in numerous organisms, including viruses, bacteria, fungi, insects, and cancer cells [9]. Despite the current heightened concern about the issue, resistance to antimicrobials is not a new phenomenon. The earliest evidence that anthropogenic activities have applied selective pressure to drive resistance development comes from the discipline of anthropology: the analysis of Nubian mummies documents the use of tetracyclines in humans as early as 350–550 CE [10]. Two millennia later, after Alexander Fleming's discovery of penicillin in 1928 [11], antibiotics rapidly became the wonder drugs of the 20th century [12], and they were mass produced and used extensively to successfully treat a variety of human

diseases. In his acceptance speech for the Noble prize in 1945 [13], Fleming predicted the widespread availability of penicillin, but also warned against the development of antimicrobial resistance as a result of inappropriate use.

Resistance may be intrinsic or acquired. Among microorganisms, intrinsic resistance is a result of the organisms not having the specific target for the antimicrobial. In contrast, acquired resistance develops as a result of genetic changes or exchanges following random mutation and horizontal gene transfer, respectively [14,15]. These genetic changes result in modifications to the targets, such that the antimicrobial no longer interacts with its target site, or in the acquisition, induction, or up-regulation of metabolic pathways that increase the degradation or removal of the pesticide from the organism [16].

3. Use of Pesticides

Pesticides encompass a wide spectrum of chemical and biological compounds that exhibit biostatic or biocidal activity used to control weeds, rodents, spiders, insects, nematodes, mollusks, and microorganisms, notably fungi, bacteria, viruses, and protists. They are used during various stages of plant production, including prior to planting, during plant growth, and post-plant-based agricultural harvest for agronomic and horticultural purposes, as well as in floriculture, forestry, recreational areas, and by home gardeners [17]. The types and kinds of available pesticide formulations, including synthetic compounds and biopesticides, are extensive and constantly growing. Typically, the active ingredient, the pesticide component responsible for biological activity, is formulated with a number of different materials, including a variety of combinations of solvents, carriers, surfactants, and buffers. For example, the European Union has approved approximately 500 different active substances in pesticides [18]. The International Organization for Standardization (ISO) lists over 1700 different active ingredients in pesticides.

FAO estimates that between 20 and 40% of global crop production is lost to pests and diseases, resulting in over 220 billion USD in losses to the global economy [19]. Thus, pesticides are critical tools in controlling diseases in plants, especially in horticulture and ornamental plant production. Their appropriate use can also improve quality, enhance yield, extend shelf life, and increase profits. They include a variety of products used as bactericides, including antibiotics, as well as fungicides, herbicides, insecticides, and plant growth regulators, among others. As such, the net global use of these products is poorly defined. Strict controls in some countries allow for the tracking of pesticide use in various sectors, while in other countries, and on a global scale, some of the best estimates for use can only be derived from proprietary sales data [20]. In 2016, the global plant protection market was estimated to represent about 63 billion USD in annual sales, with an increase predicted at 5% annually for the next 5 years, the largest portion of growth attributable to the Asian Pacific region [20].

Given that fungal and bacterial diseases account for such large production and economic losses in plant agriculture [21], antimicrobials (those agents that have biocidal or biostatic effects on bacteria, fungi, viruses, and protists, including oomycetes), are among the most commonly used classes of pesticides, second only to herbicides. Many bacterial and fungal disease pressures are higher in tropical than temperate parts of the world, especially in low- and middle-income countries (LMICs).

For many high-income countries (HICs), approval for the sale and use of pesticides, also called plant protection products, including fungicides and bactericides is regulated based on efficacy evaluation and risk assessments for human health and the environment. In contrast, regulations for pesticide use in LMICs may be less stringent or not fully enforced due to capacity reasons. The average number of staff working in the national pesticide registration authorities in these countries is three, as opposed to 700 in the United States or 150 in the United Kingdom (FAO survey 2013, 109 countries). In such countries, lack of education regarding the proper use of plant protection products may cause crop producers to apply these materials in error with respect to the approved indication for specific crop, dosage, timing, or specific pathogen.

For decades, antimicrobials (please refer to the Glossary) have been the cornerstone of the control and treatment of many diseases in humans, animals, and plants alike. Bacterial and fungal plant pathogens rarely infect animals and humans, although a few, including *Burkholderia* spp. and *Pseudomonas aeruginosa*, may cause disease in immune-compromised people or animals. Several plant pathogenic fungi in the genera *Fusarium*, *Aspergillus*, and *Claviceps*, among others, produce toxins that are harmful to humans and animals. Although they are not considered to be major cause of plant disease, *Aspergillus* species are responsible for several disorders in various plant and plant products. The most common species are *A. niger* and *A. flavus*, followed by *A. parasiticus*, *A. ochraceus*, *A. carbonarius*, and *A. alliaceus*. They can contaminate agricultural products at different stages, including pre-harvest, harvest, processing, and handling. Changes due to spoilage by *Aspergillus* species can be of a sensorial, nutritional, and qualitative nature, such as pigmentation, discoloration, rotting, and the development of off-odors and off-flavors. However, the most notable consequence of their presence is mycotoxin contamination of foods and feeds. As they are opportunistic pathogens, most are encountered as storage molds on plant products. Saprophytic fungi, such as *Aspergillus fumigatus*, that decay plant tissues can also be opportunistic pathogens [22].

Nevertheless, the increased recognition of contamination of fruits and vegetables with zoonotic pathogens (such as *Salmonella* spp. and Shiga toxin-producing *Escherichia coli*) and their role in foodborne disease outbreaks, as well as the emergence of resistance in *A. fumigatus* (a species causing aspergillosis in humans) to azole fungicides structurally similar (i.e., of proven chemical homology) to those used widely in crop production, has prompted a growing interest in One Health; the concept that the actions and activities in the plant, animal, and human health sectors, as well as the environment, interact and influence the health of the other sectors [23].

3.1. Antimicrobials in the Environment

The environment, especially soil, is considered to be a primary reservoir of microorganisms that produce antimicrobials [24]. Antimicrobial production is believed to have evolved 500 million years ago as a mechanism for fungi and bacteria to reduce the population levels of surrounding microorganisms and, therefore, increase the availability of nutrients and other resources in the immediate environment [25]. Consequently, to avoid self-destruction, it was also critical that antimicrobial resistance, either intrinsic or acquired, co-evolved with the production of antimicrobials. Antimicrobials produced by saprophytic and soilborne organisms have been exploited for human, animal, industrial, and agricultural purposes. They have also served as a model for the development of synthetic antimicrobial agents. It is hypothesized that only a small fraction of soil-derived antimicrobial agents of microbial origin have been identified [26]. New antimicrobials continue to be identified from soil [27]. The presence of such a vast and diverse pool of antimicrobial agents produced by soil microorganisms would indicate an equally large pool of genes that encode resistance.

Point-source contamination of industrial waste from sources, such as pharmaceutical manufacturing or hospitals, or wastewater discharge, may contribute antimicrobials directly into surface waters, in some cases at levels that approach therapeutic concentrations [28]. Several non-point sources of antimicrobial (antibiotics and fungicides) contamination have also been identified, notably from agriculture. For example, up to 80% of some antimicrobials used in animal agriculture are excreted non-metabolized, and are thus present in an active state in animal waste [29]. Run-off from livestock grazing areas, or from fields where manure is applied as a soil amendment, may also contaminate waters with antimicrobials [30]. Water in the plant production environment can also serve as both a reservoir and a vehicle of transmission of AMR organisms and genes, via the same routes noted above [31].

A large number of naturally occurring products from plants (extracts, oils, small molecules) have antimicrobial properties, and may be responsible for selecting the composition and diversity of the microflora of the phyllosphere and rhizosphere [32]. At one time,

the idea of producing antimicrobial peptides using genetically engineered plants, in a process called biopharming, was promoted [33,34]. Moreover, naturally occurring organisms in the phytobiome may both produce antimicrobials and/or serve as reservoirs of AMR genes. For example, certain strains of the plant pathogen *Erwinia carotovora* (*Pectobacterium carotovorum* subsp. *carotovorum*) produce carbapenem, a potent antibiotic considered a high priority, critically important antimicrobial by WHO [35].

In some production systems, animal and human waste is intentionally applied to fields or crops. These products may contain organisms with AMR determinants in their genetic material and serve as reservoirs for genetic exchange among microorganisms in the environment [36]. Fungicides are widely applied post-harvest to fruits and vegetables to extend shelf life and reduce post-harvest losses [37]. Moreover, some researchers have explored the use of antimicrobial washes and packaging, including the use of copper-containing products, penicillins, tetracyclines, and ciprofloxacin, as methods to control post-harvest losses in vegetables [38]. Although these studies were experimental, it is possible that some processors are already including these approaches to control losses in the absence of cold chain control. Coating the inside of growing containers with copper compounds is a common practice in landscape nurseries to prevent root circling of trees and shrubs [39].

Following exposure, antimicrobials may persist on plants, resulting in food safety risks associated with toxicological, immunological, or allergic reactions. Pesticide residues have long been a toxicological food safety concern, and HICs have extensive monitoring programs for their presence in the food chain, which is not necessarily the case in LMICs.

More recently, the use of pesticides and resulting residues have raised new concern due to the impact of antimicrobials and antimicrobial resistance on human health. If used improperly, antimicrobial residues may remain on fruits up to the time of consumption, at levels that pose a threat to human health. Although rare, antimicrobial residues in food can also cause life-threating allergic reactions among susceptible individuals [40,41]. Residues of streptomycin have been reported from honey bee hives located near pear orchards sprayed with this antibiotic for disease treatment [42]. There is a single report of a young child being rushed to the emergency room in anaphylactic shock [43] following the consumption of a blueberry pie. The source of the allergic reaction was suspected to be contaminated blueberries used in the pie. Several species of plants can take up and concentrate antimicrobials in the edible portions of their leaves, roots, fruits, and seeds/grain, further exacerbating the problem [44–47].

Of ever-growing concern is the impact that the addition of antimicrobials in the plant production environment can have on the selection of antimicrobial-resistant organisms in the food supply. In some instances, concentrations of antimicrobials in environmental niches may approach high levels [48,49]. There is also growing concern that exposure to low concentrations, 10–500 times lower than clinical minimum inhibitory concentrations (MICs), of disinfectants and antimicrobials may be strong drivers for acquired resistance, both by increasing the rate of mutations and stimulating horizontal gene transfer [50]. This raises the concern of selection occurring in foods and in the gastrointestinal tract following consumption, and the possible need to re-evaluate the maximum residue levels (MRLs, the highest level of a product residue that is legally tolerated in or on food or feed when that product is applied correctly) for several antimicrobials.

3.2. Antibiotic-Resistant Organisms in the Plant Production Environment

AMR organisms and antimicrobial resistance genes are widespread in the environment, including plant production systems, for the reasons explained in Section 2. Indeed, the vast majority of antimicrobial resistance genes present in pathogenic bacteria can be traced to soil microorganisms [51]. AMR organisms can also be introduced and selected or amplified in pre- and post-harvest food production systems as a result of agricultural practices.

One potential source of antimicrobial resistance genes in horticulture production that received considerable attention in the early 1980s was the transfer of such genes

from genetically modified plants to endogenous bacterial flora. This literature has been extensively reviewed [52]. Briefly, many antimicrobial resistance genes, notably *aph(3′)-IIa* (also known as *nptII*), conferring kanamycin and neomycin resistance, and *ant(3″)-Ia* (also known as *aadA*), conferring streptomycin and spectinomycin resistance, have been used as selectable markers in transgenic plants. These genes may remain intact for extended periods in soil and decaying plant matter. In plant transformation, these genes are stably integrated into the host genome, and are not on mobile genetic elements; as such, they are unlikely to be exchanged into the genomes of endogenous soil bacteria because they do not have the sequence homology flanking the resistance genes required to facilitate homologous recombination. Thus, although transfer is theoretically possible and reproducible under highly controlled laboratory conditions, it has not been observed in the field.

Despite the remarkably low likelihood of genetic transfer, taking into consideration the potential impact on human health and the use and need of particular drugs in medicine, the Scientific Panel on Genetically Modified Organisms recommended to the European Food Safety Authority that the use of antimicrobial resistance marker genes be classified into three categories (Table 1) [53]. These initial recommendations were upheld following a second review in 2009 [54]. As analytical methods improve and more data become available, these recommendations should be revisited.

Table 1. European Food Safety Authority (EFSA)-approved uses of antimicrobial resistance genes in genetically modified organisms (GMOs).

Group	I	II	III
Restriction	None	Field trials, not for market products	Not to be used
Examples	Kanamycin, hygromycin	Chloramphenicol, ampicillin, streptomycin, spectinomycin,	Amikacin, tetracyclines

More recently, the focus has been on the contamination of plants with phytopathogens, zoonotic agents, and organisms indicative of microbial contamination (e.g., *E. coli*). Wildlife intrusion and defecation into fields and irrigation water, and the contamination of crops by workers or contaminated equipment, are frequent routes of unintentional foodborne contamination [55]. Biocontrol agents intentionally added to crops to control diseases may harbor antimicrobial resistance genes and serve as a reservoir for transmission [56]. The public health concern of fruits and vegetables contributing to the epidemiology of antimicrobial-resistant infections in humans is supported by (1) the presence of antimicrobial-resistant microorganisms from fresh fruits and vegetables consumed raw, (2) the colonization of humans (and animals) with bacteria derived from food and feed, and (3) foodborne outbreaks associated with antimicrobial-resistant bacteria linked to the consumption of fresh fruits and vegetables.

Multiple cross-sectional studies from around the globe have reported a number of different antimicrobial-resistant bacterial contaminants and zoonotic pathogens present on fresh fruits and vegetables [57]. Epidemiological studies evaluating the carriage and colonization of the gastrointestinal tract with antimicrobial-resistant organisms among individuals consuming vegetarian diets support the role of fruits and vegetables in contributing to the diversity of antimicrobial-resistant gastrointestinal microflora [58–62]. In an experimental animal model study, nasal and fecal bacterial flora of sheep showed higher prevalence of streptomycin-resistant and multi-drug-resistant *E. coli* in animals grazed on pastures treated with streptomycin compared to animals grazing on untreated controls [63]. Finally, foodborne disease outbreaks have been linked to mangos and cucumbers contaminated with salmonella resistant to streptomycin and tetracycline, respectively [64–66].

The studies cited above provide evidence that antimicrobial resistance is a public health concern of paramount importance, and that plant-based agriculture is one of the many contributors to the complex ecology of the problem. To develop science-based One Health approaches to control antimicrobial resistance, the extent that horticultural

practices, specifically the use of antimicrobials in pre-harvest production, impact the global emergence, survival, and transmission of antimicrobial resistance in human and animal populations and the environment, requires additional definition. Likewise, gaining a better understanding of how animal and environmental factors may impact the contamination of fruits, vegetables, nuts, legumes, pulses, and grains is critical.

4. Resistance to Pesticides Associated with Antimicrobials

Many important plant diseases of bacterial and fungal etiology are amenable to treatment with bactericides/fungicides. On the global scale, the extent that fungicides are used on crops is unknown. In the EU, bactericides, including antibiotics, are restricted to a few agents, and non-bactericidal antibiotics are no longer approved [18]; however, fungicides are widely used. In the United States, over 4000 different antimicrobial pesticide products containing over 275 different active ingredients are available on the market [67]. This includes reagents with antifungal and bactericidal activity. Antibiotics represent the subset of antimicrobial compounds with static or cidal activities against bacteria. This review will include (1) classical antibiotic drugs used in plant production and medicine, (2) copper-containing pesticides, because of the possibility of co-selection for AMR, and (3) fungicides with structural homology to drugs used in human and veterinary medicine.

4.1. Antibiotics

There are three classes of antibiotics regularly used in plant production that are also routinely used to treat animal and human diseases, known as: aminoglycosides, tetracyclines, and quinolones. In addition, other antibiotics are used occasionally, or on an experimental basis, to control plant diseases. Both the World Health Organization (WHO) and the World Organization for Animal Health (OIE) have classified antibiotics (Table 2) based on their importance for use in human and animal health, respectively [35,68].

Table 2. Classification of importance of antimicrobials by the World Health Organization (WHO) and the World Organization for Animal Health (OIE).

	Examples	OIE	WHO
Aminoglycosides	Streptomycin, kasugamycin (in plant protection only)	Very Critically Important Antimicrobial (VCIA)	Critically important
Tetracyclines	Oxytetracycline	VCIA	Highly important antimicrobial
Quinolones	Oxolinic acid	VCIA	Highly important antimicrobial

4.2. Aminoglycosides

Aminoglycosides are a class of antimicrobials originally derived from bacteria in the genera *Streptomyces* and *Micromonospora*. Several synthetic derivatives or modifications are also now produced. Their bactericidal activities are mediated by binding to the 16S ribosomal subunit and inhibiting prokaryotic protein synthesis [69]. The spectrum of activity of aminoglycosides includes both Gram-negative and Gram-positive bacteria. They have been used in human and veterinary medicine since 1945 to treat a wide variety of common diseases in humans and animals.

4.2.1. Streptomycin

In 1943, the discovery of streptomycin was considered a hallmark event as it provided a treatment for tuberculosis. It gained popular use in human medicine, and by 1955 received approval for use in plant agriculture in the US. Today, it is probably the most widely used antibiotic in horticultural production. Streptomycin use is approved in the US, Canada, Israel, New Zealand, Mexico, and some Central and Latin American, as well as Asian

countries. As of June 2016, the Chinese certificate for streptomycin use in agricultural production expired and has not been renewed [70]. Elsewhere, streptomycin is used on a variety of crops for the treatment of bacterial diseases, primarily fire blight (*Erwinia amylovora*) in fruit trees, but also in limited applications against species of *Xanthomonas*, *Pectobacterium*, *Erwinia*, *Agrobacterium*, and *Pseudomonas* in other crops. In January 2021, the U.S. EPA approved a supplemental label, expiring in April 2023, for streptomycin use on up to 100,000 acres of citrus in Florida to manage citrus greening (huanglongbing; *Candidatus* Liberibacter spp.). However, the EPA's ruling has been challenged in the courts by environmental and farm worker groups [71].

Resistance to streptomycin is well-documented [72]. The first reports of bacterial resistance to streptomycin were published as early as 1945 [73]. Due to widespread antimicrobial resistance to streptomycin among Enterobacteriaceae, it has limited use in human medicine [72]. There are several mechanisms of resistance to streptomycin, including altered ribosomal binding, reduced uptake, and enzymatic degradation. High-level, spontaneously acquired resistance is typically mediated through mutations of the gene encoding the ribosomal protein S12, known as rpsL [74,75]. In phytopathogens, this mutation is almost exclusively found in codon 43 [76].

Transferable resistance to streptomycin and other aminoglycosides is mediated by the following three distinct classes of aminoglycoside-modifying enzymes: N-Acetyltransferases (AAC), O-Adenyltransferases (ANT), and O-Phosphotransferases (APH) [72]. Some of these enzymes are active against several different antibiotics within the aminoglycoside class, whereas others, such as StrA (APH(3′)′-I) and StrB (APH(6)-Id), exhibit activity only against streptomycin.

To date, either the point mutation in codon 43 or the presence of *strA* and *strB*, also known as *aph(3″)-Ib* and *aph(6)-Id*, respectively, confer the majority of streptomycin resistance described in phytopathogens [77,78]. The gene *aadA2*, encoding resistance to streptomycin and spectinomycin, was identified in a *Pseudomonas* isolate obtained from a Michigan apple orchard [79,80]. Over 50 different aminoglycoside resistance gene variants can be found in soil bacteria, pathogens, and commensal organisms of human and animals [81], suggesting the potential that other aminoglycoside-altering enzymes may be discovered in bacteria isolated from the plant production environment. Many streptomycin-resistant phytopathogens have been isolated for which the molecular mechanisms underlying their resistance are yet to be characterized [82,83]. Other possible mechanisms of aminoglycoside resistance among plant pathogens may include the presence of efflux pumps or ribosomal altering enzymes (e.g., methylases) [84]. The presence of the latter among human clinical isolates is a growing concern.

In all the *Erwinia amylovora* isolates evaluated, *aph3 and aph6* are located in tandem on a few plasmids (pEa8.7, pEa34, pPEU30), or on the non-conjugative plasmid pEA29 that is universally conserved within *Erwinia amylovora* [76]. Of note is that aminoglycoside resistance genes are encoded on an integron within transposon Tn*5393* that facilitates gene transfer and integration at different locations within cells [78].

Streptomycin resistance has also been reported among other phytopathogens and soil organisms in the plant production environment [85,86]. The strA-strB gene cassette (probably involved in conferring high resistance levels to streptomycin) is carried on an integron within the Tn3-family transposon Tn*5393*. The *suIII* gene, responsible for sulfonamide resistance, is often linked with *strA-strB* [87]. Genetically linked resistance genes are susceptible to co-selection pressure by streptomycin exposure. Sundin and Bender [88] described the genetic linkages between the genes responsible for streptomycin and copper resistance among phytopathogens, and how the use of one of these agents may co-select for the other.

4.2.2. Gentamicin

Gentamicin, another aminoglycoside antibiotic used in plant agriculture, differs from streptomycin regarding the structure of the heterocyclic ring, and the hydroxyl substitu-

tions that are linked to the amino sugars. As such, gentamicin has a slightly different mechanism of action, spectrum of activity, and clinical use than streptomycin. Gentamicin was discovered in 1963, and by 1967, plasmid-associated resistance was reported among human isolates [72,89]. It was approved for the treatment of blight in apples and pears, and of some diseases in vegetables in parts of South and Central America and in Mexico.

Unlike for streptomycin, ribosomal mutations are seldom responsible for resistance to gentamicin [84]. The enzymes that confer gentamicin resistance are different from those responsible for the inactivation of streptomycin, most of which are encoded on mobile genetic elements, such as plasmids, integrons, and transposons [90]. Albeit, that gentamicin resistance is usually included on human and animal diagnostic screening panels and in national surveillance programs (AGISAR) [91], there are limited reports of gentamicin resistance prevalence among bacteria of plant origin [84]. One identified survey on this topic reported the presence six genes (aac(3)-I, aac(3)-II/VI, aac(3)-III/IV, aac(6′)-II/Ib, ant(2″)-I, aph(2″)-I) frequently responsible for gentamicin resistance in orchard soil and the rhizosphere of several different kinds of plants [36]. Collectively, all of the tested genes, except aac(3)-III/IV, were identified in at least one or more of the samples collected.

4.2.3. Kasugamycin

Kasugamycin, another aminoglycoside antibiotic used in plant agriculture, was first described in 1965 [92]. It is used mainly in rice and some vegetable and fruit production. Its molecular structure, and hence its spectrum of activity, differs considerably from the other aminoglycosides. Unlike the other aminoglycosides, kasugamycin is bacteriostatic, not bactericidal. Since it does not exhibit strong antibiotic activity against pathogens of clinical importance to humans and animals, it is not used in veterinary or human medicine [93]. In contrast, possibly due to differences in transmembrane transport present in phytopathogens, it is used in crop protection for the treatment of seedling and grain rot in rice caused by *Burkholderia glumae*; bacterial diseases of certain vegetable crops, kiwifruit, citrus, coffee, and tea; and as an alternative treatment to streptomycin and gentamicin for fire blight in pome fruits [94]. It is sold in over 20 countries; in the US its labeled use is limited to the management of fire blight, bacterial spot (*Xanthomonas* spp.) and bacterial canker (*Clavibacter michiganensis* subsp. *michiganensis*) in tomatoes and peppers, and walnut blight (*Xanthomonas campestris* pv. *juglandis*).

Resistance to kasugamycin is mediated directly through mutations in the 16sRNA gene, the site of binding, or indirectly through mutations in *ksgA*, a dimethyltransferase that targets the 16sRNA at the site of binding [94]. Kasugamycin resistance can result in low-level cross-resistance to gentamicin and kanamycin [95]. Therefore, ribosomal mutations that contribute to kasugamycin resistance may indirectly lead to gentamicin- and kanamycin-resistant bacteria in the environment [95]. In addition, mutations in other genes (*ksgB*, *ksgC*, and *ksgD*) also result in decreased sensitivity to this drug. The mechanism of *ksgD* mutational resistance is not determined [96]. However, it is known that *ksgC* alters the level of ribosomal protein expression [97], whereas *ksgB* encodes a Multidrug and Toxic compound Extrusion (MATE) efflux pump (GenBank: KU884609), and mutations in this gene result in resistance. In addition, mutations in the ABC-importer locus also result in resistance [98]. These former mechanisms of resistance are not considered mobile.

In contrast, the gene *aac(2′)-IIa* that encodes acetyltransferase AAC(2′)-IIa has been described in kasugamycin-resistant isolates of *B. glumae* and *Acidovorax avenae*. Although preliminary experiments did not demonstrate the transmission of this gene under laboratory conditions, identical surrounding nucleotide sequences have been found in temperate bacteriophages, plasmids, and other genomic elements associated with horizontal gene transfer, indicating the potential for the transmission of this resistance gene [94].

4.3. Tetracyclines

The molecular structure of tetracyclines, as the name would imply, is composed of four fused cyclical rings with attached functional groups [99]. These naturally derived

and semisynthetic molecules bind to ribosomes, preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor and thereby inhibiting protein synthesis in both Gram-positive and Gram-negative bacteria. Since the late 1940s, these drugs have been used to treat a wide range of infections in animals and in people. In plants, in addition to foliar application, it may also be injected into the trunks of trees to treat yellowing diseases and phytoplasma [100]. Oxytetracycline is approved for horticultural use in Mexico, Central America, and at least eight other countries. Presently, in the United States, it is registered for use on pears and apples for fire blight and peaches and nectarines for bacterial spot (*X. campestris* pv. *pruni*) management, as well as for limited use to combat huanglongbing and bacterial canker (*X. campestris* pv. *citri*) in citrus.

Resistance to tetracyclines is a recent phenomenon associated with their widespread use. For example, although resistance to tetracycline is common among Enterobacteriaceae today, this was not always the case. Analysis of over 400 isolates collected prior to 1950 identified a resistance prevalence of <2% among clinical isolates [101]. Resistance, as for other antibiotics, may be mediated via several mechanisms. In theory, changes in the ribosomal binding sites or alterations in membrane permeability or efflux capacity, as a result of spontaneous mutation, will reduce sensitivity to tetracycline compounds. However, the best-studied and most common mechanisms of resistance are a result of the acquisition and regulation of *tet* genes, most of which are found in a broad range of mobile genetic elements (MGE) that encode the proteins responsible for ribosomal protection, enzymatic degradation, or efflux. The association of *tet* genes with MGE explains their widespread distribution and frequent exchange. Due to their presence within mobile genetic elements, *tet* genes are often clustered with other antimicrobial resistance genes.

Despite its use in plant production, only a few tetracycline-resistant (Tc^r) plant phytopathogens have been reported [102]. When present, tetracycline resistance among Gram-negative bacteria isolated from the phyllosphere of apples was typically encoded on plasmids co-encoding Tn5393 elements [79]. Field surveys conducted in United States orchards in 1984, 1991, and 1999 all failed to identify tetracycline-resistant bacteria. The reasons for the absence of Tc^r in plant pathogens are not known. In contrast, Tc^r and tetracycline resistance genes are frequently found in the phylloplane, as well as soil, human waste, and animal manure [103].

4.4. Quinolones

Oxolinic acid is a first generation quinolone antibiotic that works by inhibiting DNA gyrase. Its spectrum of activity is primarily against Gram-negative bacteria. Its use is in human and veterinary medicine, especially for the treatment of diseases of finfish in aquaculture production. For horticultural purposes, it is considered an alternative to streptomycin and oxytetracycline for the treatment of bacterial diseases, reportedly used in Israel and Japan. Its use for plant production in other countries is unknown. Isolates of *B. glumae* with reduced sensitivity to oxolinic acid have been reported from Japan [104] and Israel [105]. Typically, resistance to quinolones is due to mutations in the *gyrA* gene, and these mutations are not transferable. However, in vitro transferable resistance and cross-resistance with other quinolones, including ciprofloxacin, was reported in an oxolinic acid-resistant *B. glumae* strain in Japan [106].

4.5. The Misuse of Antibiotics

Given the burden of bacterial plant pathogens and the development of resistance to currently used antibiotics, there is a constant search for new treatments for plant diseases. For example, there is renewed interest in the use of penicillin for the treatment of citrus greening [107]. Other antibiotics that are not approved for horticultural use may also be applied by producers, generally in parts of the world in which antimicrobial sale and use is not highly regulated. In some regions, antimicrobials are readily available without governmental or professional oversight, and used in the self-treatment of human illnesses and infections, as well as unauthorized and uncontrolled use in livestock, poultry, and

aquaculture production for disease treatment, control, and growth promotion [108]. The extent of intentional, but unauthorized, application of antibiotics on crops is unknown. The presence of antibiotic residues on plants could be a result of intentional application, or, more likely, the uptake of the antimicrobial from soil amended with manure from antibiotic-treated animals. In the latter case, the types of antimicrobials applied to the fields are dependent upon the species of animal from which the manure is derived, and the treatment time and dosage prior to manure collection and application, emphasizing the need for good management practices.

4.6. Antimicrobial Use Selecting for Resistance

The extent to which the use of streptomycin and other antimicrobials in horticulture contributes to the emergence of AMR in plant pathogens and other microorganisms in the environment, including zoonotic pathogens, is not well understood. Clearly, the genes for transmissible resistance to the above-mentioned agents are frequently present in the environment (waste, soil, and water), including on farms where antimicrobials have, and have not, been used. The results of several scientific reports on the subject are listed in Table 3.

The heterogeneity of the methods used, for example, in the measurement of different outcome variables (resistance in phytopathogens, resistance in culturable environmental organisms, presence of resistance genes, changes in microbial structure, etc.), the differences in timing of sample collection following antimicrobial application, and the limited number of controlled studies, preclude the possibility of a robust, formal meta-analysis of the subject. However, the data collectively indicate a transient selection of resistant organisms in the plant production environment following antimicrobial application. The factors that govern the selection and persistence of AMR organisms in the plant production environment are poorly understood, but may be similar to those observed in animals. A short-term burst, or transient environmental peak, in antimicrobial resistance following antimicrobial exposure is consistent with that observed in animals undergoing treatment and upon treatment cessation, wherein the reversion to antimicrobial sensitivity among the background intestinal flora occurs in a predictable fashion shortly after treatment is stopped [109]. There is poor evidence of the cumulative effects of selection of antimicrobial resistance following long-term, repeated application of antimicrobials.

Table 3. Impacts of antimicrobial use in horticulture on antimicrobial resistance.

First Author	Key Findings	Reference
Tolba	• High StrR in agricultural site without str treatment history • Decreased diversity in str-treated soil • Horizontal strA and strB transfer regardless of str treatment • Time since last str treatment not reported	[110]
Heuer	• Gentamicin resistance prevalence more frequent in treated plots and plants than untreated	[36]
van Overbeek	• ant(6)-1 and aph(6)-1c recovered from str-treated soil but not control • aph(3″) -1, ant(3″)-1 and ant(6)-1 recovered from Cu-treated soil, but not controls • ant(3″)-1 recovered from control, but not str-treated soil	[111]
Manulis	• Decreased use of str associated with decreased prevalence str-resistance	[105]
Popowska	• aad(A) only detected in orchard soil among other several different types tested	[112]
Yashiro	• More str-resistant bacteria from non-sprayed orchards (6 weeks after str application) • No effect of long-term treatment on microbial community structure	[113]
Duffy	• Occasional increases in strA, strB, IS1133, and tetB, tetW in treated vs. untreated orchards	[114]

Table 3. *Cont.*

First Author	Key Findings	Reference
Shade	• Phylogenetic diversity lower on trees treated with streptomycin	[115]
Walsh	• No effect of str treatment on abundance and diversity of bacterial species when measured 2 weeks after treatment	[116]
Shade	• No detectable effect of str on community structure when measured 8–9 days after str treatment.	[117]

Resistant strains may be outcompeted in the environment due to fitness costs associated with resistance. Isolates of *Erwinia* transformed with large plasmids conferring tetracycline resistance were less stable than wild-type tetracycline-sensitive strains [118,119]. Likewise, oxolinic acid-resistant strains of *E. amylovora* and *B. glumae* were also less fit [104,120]. Furthermore, it has been suggested that antimicrobial pesticide use in horticulture can result in limited selection for AMR organisms because of rapid photodegradation, soil adsorption/deactivation, and considerable dilution, depending on the compound applied [80].

4.7. Metals

A number of metals, notably copper and zinc, and arsenic, a metalloid, contaminate the environment from their past use as biocides in agriculture, irrigation from deep wells, wood preservation, and warfare. For example, copper, in the form of $CuSO_4$, is intentionally applied to grapes and many other crops to control various fungal and bacterial infections. $CuSO_4$ and zinc oxide are frequently added to animal feeds to control disease and improve growth, especially in young animals. Other elements, such as cadmium, chromium, molybdenum, nickel, tin, and vanadium are added to livestock and poultry diets as micronutrients, and unabsorbed metals are excreted in the feces. As such, these metals accumulate in the soil amended with manure from the animals fed these products. In addition, chemical fertilizers intentionally added to the soil may be contaminated with small amounts of lead and cadmium. Recently, the associations between heavy metal use and antimicrobial resistance have been reviewed [45].

4.8. Copper, Zinc, and Arsenic

Copper is among the most widely used antimicrobials for treating plant diseases, even in organic production systems (Figure 1). At the same time, there are a number of more important inputs of copper (and zinc) into horticultural systems. Nicholson et al. calculated inputs from agricultural lands in England and Wales for the year 2000 [121].

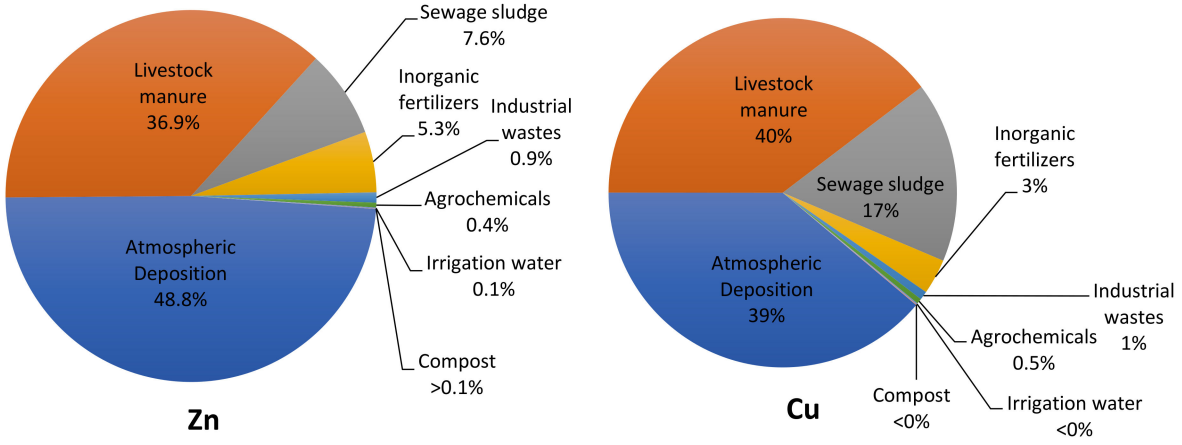

Figure 1. Sources of Cu and Zn on agriculture lands. Industrial waste includes food waste, compost, and waste from paper and textile industries.

Notably, non-atmospheric sources contributed more than 50% and 60% of all depositions of zinc and copper, respectively. It is important to note that in countries where agrochemicals or inorganic fertilizers are more widely used, this attributable fraction may increase. For example, in Italy, on average, viticulturists apply 14 kg of copper fungicides per hectare per year on vineyards [122]. Likewise, in regions where livestock manure and sludge are more commonly used, or where the concentration of these metals is higher in manure and sludge, the intentional addition on zinc and copper may also increase.

Arsenic can also be present in soil and water used for horticulture. In the past, arsenic-containing pesticides and herbicides were extensively used. Dimethylarsenic acid, "Agent Blue", was sprayed over crops and forests by United States military forces in Viet Nam as a defoliant at rates 10-fold higher than used domestically. Other arsenic-containing insecticides and herbicides were approved for use in many countries for horticultural purposes, and, although their approval has been discontinued in many countries, they still may be used in some LMICs [123,124]. Irrigation water may be a source of arsenic contamination in many parts of the world, notably South and Southeast Asia [125]. As with copper and zinc, animal manure may also be a source of arsenic. Arsenic-containing medications are routinely fed to chickens to control disease and promote growth, with most of the product being excreted unchanged in the feces [126].

Aside from the toxic effects of these elements on plants, animals, and people, there is growing concern that these metals have the potential to co-select for resistance in bacteria. The co-selection of resistance in bacteria to metals and antibiotics has been documented [4,127]. A large number of genes have been confirmed to confer resistance to metals among a wide spectrum of bacterial species [128]. As with antimicrobial resistance genes, metal resistance genes may be either chromosomal or plasmid-encoded. Copper resistance in *X. campestris* and *Pseudomonas syringae* is encoded on large conjugative plasmids [129]. Resistance to copper in *Xanthomonas* spp. causing bacterial spot in tomatoes and peppers is common, although the prevalence in resistant populations may be species-dependent [130].

Of concern is the possibility of selection of AMR bacteria through the processes of co-resistance, cross-resistance, and co-regulation with metals [4]. Pal and coworkers [131] conducted an extensive analysis of the associations between antimicrobial and metal resistance genes. Bacteria harboring metal and biocide resistance genes were more likely to also encode antimicrobial resistance genes than those without. Bacteria resistant to both metals and antimicrobials were commonly present in diverse environments, with bacteria of plant origin having the highest relative abundance of resistance genes per genome compared to bacteria from other sources, such as domestic or wild animals, and humans. Co-resistance can occur when the genes for resistance to antimicrobials and metals are both present in a bacterium, as found in only approximately 5% of bacterial isolates recovered from plants and soil. No bacterial isolates of plant or soil origin harbored genes for these two distinct resistance elements on the same plasmid, thus limiting the current role of co-selection by metal for the horizontal gene transfer of resistance genes. Nevertheless, plasmids co-encoding for metal and antimicrobial resistance have been identified in humans and animals. For example, in *Enterococcus faecium*, copper resistance (*tcr*), macrolide resistance (*erm(B)*), and glycopeptide resistance (*vanA*) are all encoded on a common plasmid. The feeding of copper sulfate to pigs, as is routinely done for health and growth promotion purposes, was found to increase *E. faecium* populations resistant to macrolides and glycopeptides [132]. In a separate example, an emerging clinically important clone of *Salmonella enterica* 4,5,12:i:- with co-resistance to copper and multiple antibiotics, is circulating throughout Spain and Southern Europe [133], a region where copper is used extensively in both horticulture and animal agriculture. Since manure and sludge are used in horticulture as a fertilizer, the use of copper for plant protection could select for antimicrobial resistance among the bacteria present in these untreated biological soil amendments.

4.9. Other Fungicides

A large number of important, production-limiting plant diseases, toxin-producing infections, and post-harvest spoilage, are caused by yeasts and molds. In the EU, several hundred substances, containing over 150 different active ingredients, have been approved as fungicides to treat and control these diseases.

In addition, fungicides are also used for non-agricultural purposes, notably as treatments in home gardening, as a biocide in paints, and as a wood preservative. The total amount of fungicides used globally is difficult to calculate because of the absence of mandatory reporting. Among the 43 countries reporting to FAO in 2014 on fungicide use, inorganic compounds, including copper, represented the single largest class (43%) of fungicides used, followed by the dithiocarbamates (17%), and the triazoles/diazoles (11%) [134] (Figure 2). Nystatin and pimaricin (also called natamycin) and tetramycin, another polyene macrolide, have been proposed for use in preventing post-harvest losses in crops [135].

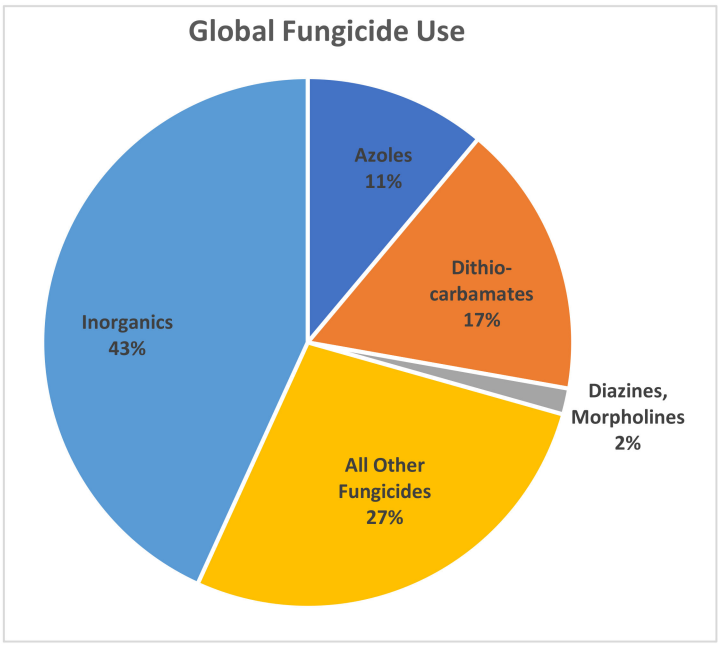

Figure 2. Frequency of use of fungicides globally (created from data in ref [135]).

In contrast, although fungi can cause a spectrum of infections in humans, ranging from superficial dermatoses and urogenital infections to systemic life-threatening illness, the fungicides available for use systemically in human and veterinary medicine are limited. Only seven different classes of fungicides are routinely used to treat fungal infections in animals and humans [136]. These are azoles, including both imidazole and triazoles; polyene macrolides (amphotericin B, nystatin, and pimaricin); flucytosine; echinocandins; and, less frequently, griseofulvin, allylamines, and iodides. Analogs of flucytosine, echinocandins, griseofulvin, allylamines, and iodides—other human and animal drugs used to treat fungal infections—are not used in crop production as fungicides. Although possible, and observed occasionally, resistance to polyene macrolides is unstable and non-transmissible [137].

4.9.1. Azoles

Azoles, notably triazole compounds, are among the most common fungicides used in veterinary and human medicine. A number of triazole-based compounds are approved for use as pesticides around the world. They are also used for wood preservation [138]. These products are heavily used in agriculture in European countries (Figure 3).

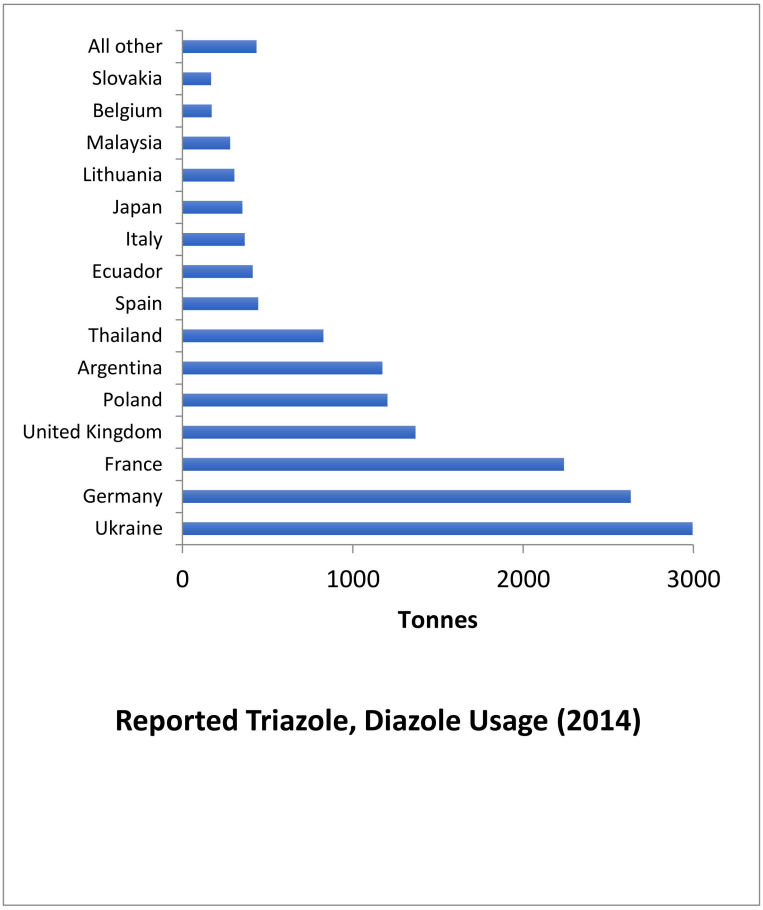

Figure 3. Reported use of azole fungicides in different countries.

All azoles work to inhibit fungal growth via the same mechanism, i.e., inhibition of a component (14α-demethylase) of cytochrome P450 that leads to the disruption of the biosynthesis of ergosterol, a critical component of all cell membranes in phyto-, human-, and animal-pathogenic fungi alike [139]. Azole resistance is due, in part, to the overexpression of the sterol demethylase gene *cyp51A*, resulting from a 34 bp tandem repeat (TR_{34}) in the promotor region, as well as a substitution of leucine to histidine (TR_{34}/L98H). Other mutations in *cyp51A* have been observed, as have clinical and environmental azole-resistant isolates lacking any mutations in *cyp51A* [140]. The environmental stability and persistence of azoles make them effective treatments for many fungal infections. At the same time, these characteristics also present problems for resistance development [141]. Resistance to azoles is documented in fungi causing disease in humans (clinical isolates), including species of *Aspergillus*, *Fusarium*, and *Candida*, among others [142].

Several different azole compounds and formulations are used to control fungal diseases in plants. The widespread and long-term use of azoles on crops has resulted in the selection of fungal phytopathogens (environmental isolates) that are resistant to them [143]. Although the exact same active ingredients are not employed for medical purposes, the structural similarities between many of these compounds (propiconazole, bromuconazole, tebuconazole, epoxiconazole, and difenoconazole) result in cross-resistance with azoles reserved for use in human medicine [144,145]. Molecular evidence points to the emergence of triazole-resistant environmental isolates of *A. fumigatus* causing aspergillosis in humans [144,146].

As is the case with several bactericides, e.g., antibiotics, some fungicides without structural homology to drugs used in medicine may impact antimicrobial resistance among animal and human pathogens. For example, 2-phenylphenol, which is used on fruits and vegetables to reduce spoilage by bacteria and yeast, selects for *E. coli* that constitu-

tively hyper-express efflux pumps, resulting in an increase in bacteria that are quinolone-resistant [147]. In a similar fashion, geraniol, a terpenoid natural plant extract, is used as a fungicide, especially on grapes. Strains of *E. coli* grown in the presence of geraniol are also selected for *marA* over-expression [148]. *MarA* is a global regulator that increases efflux pump activity, including efflux pumps that export antimicrobials out of the cell, thus rendering the bacteria resistant to many drugs. In contrast, other researchers have found that geraniol can inhibit some efflux pumps and decrease antimicrobial resistance in some bacteria [148].

4.9.2. Dithiocarbamates

This class of fungicides has been used in horticulture since the 1940s [149]. Their mechanism of action involves the inhibition of the metal-dependent and sulfhydryl enzyme systems common to both fungi and bacteria [150]. As a xenobiotic substance that impacts bacterial metabolism, it is logical to assume that evolution has or will select for bacteria capable of degrading, inactivating, or removing the compound from the cell; however, this has not been described in the literature. Curiously, one study found that the overexpression of an ABC transporter in *Aspergillus nidulans* that mediated resistance to most major classes of fungicides paradoxically resulted in increased sensitivity to dithiocarbamate fungicides [151]. The upregulation of ABC transporters is a common mechanism of resistance to antibiotics among bacteria.

4.9.3. Others

In addition to azoles, dithiocarbamates (and the copper- and arsenic-containing fungicides discussed above), there are many other active ingredients included in fungicide formulations. These compounds, such as dicloran (an aromatic hydrocarbon) and iprodione (a dicarboximide), have mutational effects on *Salmonella* sp. or exhibit inhibitory activity on nitrogen and carbon cycling activities, signal transduction, and growth in soil bacteria [152,153]. Under laboratory conditions, the antimicrobial resistance pattern of *Staphylococcus aureus* was increased in the presence of captan, a commonly used phthalimide fungicide [154,155].

4.10. Fungicide Resistance Action Committee (FRAC)

FRAC (www.frac.info, accessed on 19 January 2022) is a technical group within CropLife International (https://croplife.org, accessed on: 10 February 2022), an association of crop protection industry members, the purpose of which is to provide guidelines for fungicide resistance management and to prolong the efficacy of fungicides at risk of resistance development in crop agriculture. FRAC also provides information on the mode of action of most active ingredients used for crop protection, as well as the risk of fungicide resistance development within fungal populations.

4.11. Herbicides

Herbicides are the most commonly used pesticides, especially with the advent of herbicide-resistant genetically modified crops. In 2014, over 574,000 metric tonnes of herbicide active ingredients were used globally [135]. For the same year, it is estimated that, worldwide, 860,000 metric tonnes of glyphosate (Roundup), a non-selective weed killer, were applied in agricultural and non-agricultural use (railroads, right-of-way) settings [156,157].

Although bacteria are not the intended target of herbicides, these chemicals can be toxic to bacteria. As with other toxic compounds, bacteria may develop resistance by reducing membrane permeability, metabolism, or efflux. For glyphosate, resistance has been described as a result of efflux via a membrane transporter and metabolism mediated by an enzyme with a single base pair mutation in the gene *aroA*, that is typically responsible for the synthesis of aromatic amino acids [158]. Of concern is that laboratory experiments have demonstrated that the exposure of *Salmonella enterica* Typhimurium and *E. coli* to several

commonly used herbicides (dicamba, 2,4,-dichlorophenoxyacetic acid, and glyphosate) changes the antimicrobial susceptibility of these organisms [159]. Moreover, bacteria recovered from field trials where penicillin was being evaluated for the treatment of citrus greening showed linkages between penicillin resistance and glyphosate-resistant bacteria under conditions of protracted glyphosate usage [107].

5. Data Needs, Recommendations and Conclusions

Despite the body of literature available on antimicrobial resistance, there remain significant gaps in our knowledge related to the use of fungicides associated with antimicrobials in worldwide horticulture, and the effects of such uses on the evolution and selection of resistance to human and animal pathogens. Relatively few antibiotics (streptomycin, oxytetracycline) are used in both horticulture and in human and animal medicine, and in developed economies, these are highly regulated. Although it represents a small fraction of total antimicrobial use in the United States, the US Department of Agriculture reported that 27.9 metric tonnes of streptomycin and oxytetracycline, and 0.7 metric tonnes of kasugamycin, were applied directly to crops in the United States in 2015 (www.nass.usda.gov, accessed on 19 January 2022). On the other hand, fungicide use in plant agriculture far outstrips its use in humans and animals. Of particular concern is the azole class of fungicides, which are widely used to treat mycoses in humans, and for which resistance is well documented. Currently azoles constitute 11% of global fungicide use. There is less information on the role of herbicides and insecticides in AMR development in human and animal pathogens, than that regarding bactericides and fungicides. This is also a knowledge gap that should be addressed, particularly as it relates to the potential effects of these products on insect–bacteria symbionts and environmental bacterial and fungal communities.

5.1. Data Needs—Accessible, Reliable Estimates of Pesticides Associated with Antimicrobial Use (AMU) Worldwide

Additional information, tools, and activities are urgently needed to better understand AMU globally. While in HICs, pesticides are highly regulated and regulations are generally well enforced, and appropriate use is backed up by educational programs in the public and private sectors, this is not the case in most LMICs. Government regulations often exist, but enforcement is lax and plant protection product users rarely have access to continuing education on pesticide efficacy, safety and appropriateness, or assistance with crop diagnostics. In many of these countries, pesticides are distributed by minimally trained local dealers. Further, the quality of the pesticides, most of which are imported, is neither monitored nor enforced, and instructions (labels) are rarely written in the local or national language of the user. These factors, in addition to the unregulated distribution of antibiotics, lead to the widespread misuse of plant protection products, subsequent environmental contamination, and potential AMR development. In addition, due to poor or completely absent surveillance on AMU in LMICs, direct data regarding usage is not available. Using a database of over 400,000 PlantWise (https://plantwise.org, accessed on 19 January 2022) crop advisor recommendations in 32 LMICs between 2012 and 2018, Taylor and Reeder [160] found that fewer than 0.4% recommended antibiotics for crop disease management. The majority of antibiotic recommendations were made in Southeast Asia, while none were made in the 12 African countries with records in the database.

Significant efforts are needed on the ground in LMICs to identify products with the potential to be associated with antimicrobials (and their quantity being sold, the areas in which they are applied, crops uses and quantities), and to conduct studies on the relationship between antimicrobial-associated pesticides and development of AMR. In the United States, for instance, statistics on pesticide use are generated from self-reporting by farmers responding to surveys or specific census requests (www.nass.usda.gov, accessed on 19 January 2022). Few LMICs have the resources to collect, process, and report data on this scale; however, targeted surveys in selected countries, with alternative funding sources, should be conducted to understand the depth of the problem and the risks locally,

regionally, and worldwide of AMR development as influenced by the use of antibiotics and other antimicrobials on crops. Additionally, there are other challenges to be addressed in developing these surveillance programs that are consistent across national borders, including the need to determine the most appropriate denominator to express trends in use; for example, the kilograms of oxytetracycline used per tonne of dates or apples produced. Further, the consistency of data reporting and accessibility to data across platforms and programs must be improved. Advances in surveillance, good practices, awareness, and strengthened government regulation and oversight for antimicrobial use and surveillance will contribute to a more effective One Health approach to combat AMR.

5.2. Data Needs—Surveillance of AMR Organisms in Horticulture and the Environment

Particularly in LMICs, systems to record AMR organisms and/or the genes associated with fruits and vegetables at the national level are virtually non-existent. This scarcity of resources demands the prioritization of the following steps. Surveillance systems should be developed in such a way that they can be integrated and harmonized with other sectors, such as antimicrobial resistance programs in humans, animals, and foods of animal origin. They should include the monitoring of produce as well as of environmental sources, e.g., run-off from fields and surface waters, and the contributions from field-applied manure—all of these should help to clarify the dynamic of the antimicrobials in plants and the environment.

In addition to antimicrobial resistance among plant pathogens, it is important to monitor animal, human, and zoonotic pathogens on plants, as well as the resistomes (the collection of all the antimicrobial resistance genes and their precursors in both pathogenic and non-pathogenic microorganisms) of other organisms in the plant production environment that may contribute resistance genes to the food chain. While the focus of concern for antimicrobial resistance has been on specific antibiotics used on a small number of horticultural crops, a broader range of plant protection products must be considered to define their roles. These should include active ingredients and potential additives with significant crop and environmental presence due to their widespread use and persistence and movement in the environment; additionally, these should be prioritized based on their mode of action/risk of resistance development in target and non-target organisms, and their use of similar or related activities in human and animal therapies. For example, understanding the risks of antimicrobial resistance development in human pathogens, such as *Aspergillus* spp., exposed in the environment and on treated crops to azoles worldwide should be a high priority. The lack of controlled quantitative studies and absence of a consensus on what the appropriate assessment measures should be (e.g., resistance in plant pathogens or specific microbial species, resistance among cultural bacteria, specific gene copy number, timing of application, samples collected, which genes to monitor, the laboratory methods used to collect this data, etc.), are critical gaps. Ideally, these issues should be considered on a global scale within the antimicrobial resistance research community, including the active input of government, the plant protection products industry, and crop farming community stakeholders. Beyond consensus on the "what" and "how" of AMR organism surveillance, new, rapid, and inexpensive tests and tools to identify plant pathogens and characterize the resistome of the plant production environment are sorely needed to establish more appropriate AMU guidelines and surveillance strategies.

5.3. Approaches to Support Judicious Pesticide Use

Biological control organisms suppress plant diseases by direct antagonism, antibiosis, competition, hyperparasitism of pathogens, or via the induction of host plant resistance. Biorational products, such as plant extracts, can suppress plant disease development through antibiosis, induction of disease resistance, and other mechanisms. Both are alternatives to synthetic pesticides, and are considered as antimicrobials to prevent and treat plant diseases. These products are considered to be of low risk to the environment and human health. Recent studies indicate a role for biological or biorational products in reduc-

ing AMU by applying them in alternation with antimicrobials, without reducing disease suppression. As more is learned about the phytobiome functions in food crop systems, more effective pre- and probiotic agents against plant pathogens may be developed, and thus reduce the need for conventional antibacterial and antifungal agents.

By far the best approach to limiting the use of antimicrobials in conventional plant production systems while maintaining their effectiveness is through the adoption of the well-established measures of "Integrated Pest Management" (IPM), a system approach designed to minimize economic losses to crops, as well as the risks to people, animals, and the environment. The main components of IPM for plant diseases are (1) accurate diagnosis and monitoring, which can also include disease modeling and predictive systems to guide the timing of pesticide applications; (2) use of disease-resistant crop varieties, including disease-resistant rootstocks in both fruit and vegetable systems; (3) exclusionary practices that prevent the introduction of pathogens into a crop, such as using pathogen-free true seed and vegetative planting material, clean irrigation water, and sanitation practices that prevent the movement of pathogens from plant-to-plant and field-to-field; (4) site selection and soil improvement to maximize plant health and minimize environmental factors that favor pathogens; (5) crop rotation and other cultural practices to prevent pathogen buildup; (6) use of biological and biorational products; and (7) judicious use of pesticides, including both antibiotics and fungicides.

While growers in HICs are aware of, and practice, integrated disease management strategies, increasing the adoption of these practices, especially in LMICs, will greatly decrease the need for antimicrobials. IPM should continue to be emphasized in grower and gardener education in high-income economies, and should be widely encouraged through governmental and non-governmental programmes in LMICs. The importance of IPM in mitigating antimicrobial resistance, and promoting food security and human and animal health, cannot be overstated.

5.4. Sustainable Production, and Its Contribution in Preventing AMR Development

Few methods are available to reduce or eliminate bacteria or antimicrobial resistance genes from fruits and vegetables consumed raw or with minimal processing. As such, the prevention of contamination, at all stages of production and processing, is of paramount importance to reduce the introduction of AMR organisms into the plant-based food chain. The development, validation, and application of additional contamination prevention strategies along the entire food chain could greatly reduce antimicrobial resistance development in foods of plant origin.

Due to the limited number of products available to effectively treat plant diseases, additional strategies to prevent and manage them should be developed, especially interventions and products with systemic effects. Valuable innovations may include the following: selective breeding to decrease host plant susceptibility to diseases or to degrade antimicrobials; research into fungicides and bactericides with modes of action not shared with drugs used in human medicine; use of effective biologicals (probiotics, prebiotics, bacteriophages) and biorational compounds; exploitation of the microbiome and soil health to control plant diseases; and more effective integrated disease and pest management strategies. Additional information is specifically needed to quantify the relationship between the use of pesticides and other influences on the selection, transmission, and persistence of antimicrobial resistance among organisms on plants and in the surrounding food production environment.

5.5. Improved Regulation on Pesticides Associated with Antimicrobials

At the heart of the matter, a paradigm shift in behavior and management is needed to reduce AMU. Awareness is key for both recognizing the severity of the problem and promoting the adoption of sustainable solution pathways. Antimicrobial resistance is a problem that affects everyone. Not only can AMR organisms reduce plant yields and economic success at all scales of production, they can also cause serious health impacts on

workers who apply antimicrobials and on their families, and on customers who consume products contaminated with antimicrobial residues and AMR bacteria or fungi. In some countries, buyers are demanding commodities produced with strong antimicrobial stewardship practices, such as treating only after a correct diagnosis, appropriate application and dosing, respecting pre-harvest intervals, and incorporating IPM practices. However, knowing and applying the best approaches to reach producers and promote change remains an obstacle to the adoption of the best practices to mitigate antimicrobial resistance. The problem regarding lack of awareness is further complicated by misinformation and the availability of products on the market that are fraudulent, substandard, or otherwise without evidence of effectiveness.

5.6. Conclusions

Genes conferring resistance to antimicrobials, including most drugs used for human and animal health purposes, are found among bacteria isolated from foods of plant origin and from fungi in the environment, plants, humans, and animals. Soil, water, insects, animal intrusion, manure as fertilizer, and human handling are probable contamination sources. The extent to which antimicrobial-associated pesticide use in plant production selects for the emergence and maintenance of AMR organisms in the plant production environment is not fully understood. Additional data, including surveillance and testing, are needed to complete comprehensive risk assessments and identify sustainable plant health practices that are less dependent upon pesticide use. The real relationship between pesticide use and AMR development should be studied and clarified. The dynamics of both antimicrobials and AMR in plants and the environment should be studied and well understood to prevent the risks of AMR in horticulture. Risk assessment of pesticides on AMR development and proper action regarding the management of antimicrobial-associated pesticides should be considered. Integrated pest management practices also help reduce the reliance on pesticides (including antimicrobials) in horticultural cropping systems. There is increasing recognition that everyone has a role to play in protecting human and animal health, as well as the environment, against antimicrobial resistance development. Raising awareness of the negative consequences of overuse of antimicrobial-associated pesticides, including antibiotics and fungicides across all sectors—pesticide users, the food industry, regulators, and the general public—helps to promote more responsible use of these products worldwide. Training users in the responsible application of antimicrobial-associated pesticides and the consequences of irresponsible use is a critically high priority in countries with developed economies and in LMICs alike.

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Glossary

Antibiotic	An antimicrobial with a spectrum of activity limited to bacteria.
Antibiotic resistance	The inherited or acquired characteristic of microorganisms to survive or proliferate in concentrations of an antibiotic that would otherwise kill or inhibit them.
Antimicrobial	Any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of viruses and species of the kingdoms Archaebacteria, Chromista, Eubacteria, Protista, and Fungi. For the purpose of this publication, we consider antimicrobials to include antibiotics (bactericides) and fungicides, and not nematicides, herbicides, plant growth regulators, insecticides, botanicals, or biological control agents.
Antimicrobial resistance	The inherited or acquired characteristic of microorganisms to survive or proliferate in concentrations of an antimicrobial that would otherwise kill or inhibit them.
Cross-resistance	The ability of a microorganism to multiply or persist in the presence of other members of a particular class of antimicrobial agent or across different classes due to shared mechanisms of resistance.
Co-resistance	The ability of a microorganism to multiply or persist in the presence of different classes of antimicrobial agents due to possession of various resistance mechanisms.
Pesticide	A substance that "prevents, destroys, or controls a harmful organism ('pest') or disease, or protects plants or plant products during production, storage and transport". The term includes, amongst others: herbicides, fungicides, insecticides, acaricides, nematicides, molluscicides, rodenticides, growth regulators, repellents, and biocides.

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