Phytopathology® • 2024 • 114:885-909 • https://doi.org/10.1094/PHYTO-10-23-0357-IA

Key Challenges

Phytopathology®
REVIEW

The Use and Impact of Antibiotics in Plant Agriculture: A Review

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Accepted for publication 8 March 2024.

Abstract

Growers have depended on the specificity and efficacy of streptomycin and oxytetracycline as a part of their plant disease arsenal since the middle of the 20th century. With climate change intensifying plant bacterial epidemics, the established success of these antibiotics remains threatened. Our strong reliance on certain antibiotics for devastating diseases eventually gave way to resistance development. Although antibiotics in plant agriculture equal to less than 0.5% of overall antibiotic use in the United States, it is still imperative for humans to continue to monitor usage, environmental residues, and resistance in bacterial populations. This review provides an overview of the history and use, resistance and mitigation, regulation, environmental impact, and economics of antibiotics in plant agriculture. Bacterial issues, such as the ongoing Huanglongbing (citrus greening) epidemic in Florida citrus production, may need antibiotics for adequate control. Therefore, preserving the efficacy of our current antibiotics by utilizing more targeted application methods, such as trunk injection, should be a major focus.

Keywords: antimicrobial, chemical application, crop protection, resistance, tree crops

Progress of Antibiotic Use in Plant Agriculture

As early as the beginning part of the 20th century, humans have depended on antibiotics to combat various bacterial diseases. The monumental discovery of antibiotics propelled our fight against human-pathogenic bacteria, which soon translated over to plant bacterial diseases in agriculture. Although the initial agricultural use for antibiotics was to control fire blight (*Erwinia amylovora*) in pome fruit, other devastating bacterial diseases, such as Huanglongbing (HLB) in commercial citrus, now rely on antibiotics to control widespread disease pressure. In this section, we will review past antibiotic use in the United States, as well as its increased importance in present-day plant agriculture.

Historical importance of antibiotics in plant agriculture

After Alexander Fleming discovered the first antibiotic, penicillin, in 1928 (Fleming 1929), human medicine changed forever. Loss of human life from bacterial diseases decreased astronomically, and overcoming lethal bacterial infections became increasingly possible (Aminov 2010). Roughly 15 years later, the equally serendipitous finding of streptomycin by Albert Schatz and Selman Waksman launched an era of bacteriological innovation (Schatz et al. 1944). The "antibiotic era" of the 1950s to 1970s—when most classes of antibiotics were discovered and characterized—played a pivotal role in significantly lowering mortality rates caused by bacterial infections (Aminov 2010). Such therapeutic success in humans quickly garnered interest in plant agriculture, specifically the pome fruit industry (Leben and Keitt 1954; Weindling et al. 1950).

Fire blight, a disease caused by the Gammaproteobacteria *Erwinia amylovora*, left many pome fruit and related ornamental growers struggling to produce yield. As early as the mid-1950s, growers began using the antibiotic streptomycin to control fire blight in commercial orchards (U.S. EPA 1992), employing as many as 20 applications per year (Stockwell 2014). Streptomycin was originally isolated from the soil-dwelling bacterial species *Streptomyces griseus* and was the first aminoglycoside antibiotic discovered (Schatz et al. 1944). The potency of streptomycin against *E. amylovora* allowed the pome fruit industry to rebound by reducing fire blight strikes per tree by as much as 98% compared with untreated controls (Norelli et al. 2003). Soon after, growers of other high-value crops (stone fruits, tree nuts, vegetables, and ornamentals) also turned to antibiotics to control destructive bacterial diseases. These diseases included bacterial spot on stone fruit

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Funding: Support was provided by the Emergency Citrus Diseases Research and Extension (grants 2019-70016-29096 and 2020-70029-33196) from the U.S. Department of Agriculture-National Institute of Food and Agriculture.

The author(s) declare no conflict of interest.

(causal agent *Xanthomonas arboricola*) and on pepper and tomato (causal agent *X. campestris* pv. *vesicatoria*), as well as crown gall (*Agrobacterium tumefaciens*) on rose (McManus et al. 2002). However, the majority of antibiotics used in plant agriculture today are applied to fruit trees (NASS-USDA 2021).

Although streptomycin treatments initially showed great success, plant-pathogenic bacteria resistant to streptomycin were reported as early as in 1962 (Stall and Thayer 1962; Thayer and Stall 1962). The prevalence and persistence of streptomycin-resistant *E. amylovora* strains led to the use of oxytetracycline (OTC), a heat-tolerant, light-sensitive member of the tetracycline class of antibiotics, which was first registered as a pesticide for use on pear and peach in 1974 (U.S. EPA 1993) and in 2008 for fire blight management on apple. The aminoglycoside kasugamycin, which lacks any use in human or animal medicine, was registered for specific uses in plant agriculture in 2018 (U.S. EPA 2018). Both OTC and kasugamycin are currently major tools to combat streptomycin-resistant phytopathogenic bacteria (Adaskaveg et al. 2011).

Diverse plant bacterial pathosystems dependent on antibiotics for management

Apple and pear growers were among the first to use antibiotics commercially—specifically streptomycin and OTC—in plant agriculture, primarily attributed to managing fire blight (Stockwell and Duffy 2012). To infect a tree and cause the fire blight disease, *E. amylovora* lands on flowering blossoms via rain, contaminated pruning tools, or honeybees and can inoculate trees by entering the pistil of the flower (van der Zwet and Keil 1979). Leaving shriveled blossoms in its wake, the bacteria can continue to spread to the rest of the shoot, leaves, and other twigs. This superficial location of bacterial entry and disease development requires prophylactic spraying of blossoms with streptomycin to prevent the onset of fire blight. The environment heavily affects *E. amylovora* epiphytic growth, which can help direct disease risk models for growers. Similarly, bacterial spot and canker of stone fruits caused by *X. arboricola* results in lesions on the fruits and leaves of susceptible cultivars and also requires preventive spraying of antibiotics and other compounds to control disease outbreaks (Christiano et al. 2010). Furthermore, *E. amylovora* and *X. arboricola* can be easily cultured, offering researchers the ability to study growth cycles, opportunities to screen different control methods, and molecular strategies to monitor antibiotic resistance development.

On the other hand, the citrus industry in Florida faces the destructive HLB disease, which is caused by the unculturable, phloem-limited '*Candidatus* Liberibacter asiaticus' (*C*Las) bacteria and results in an incurable and systemic infection of citrus trees. Following deposition by the Asian citrus psyllid (*Diaphorina citri*) vector, the *C*Las pathogen survives in the vasculature (phloem) of the tree, protected from external conditions (Bové 2006). Although chemical control of Asian citrus psyllids has aided the citrus industry for years, insecticide resistance in populations is reducing their efficacy (Tiwari et al. 2011). For the HLB pathogen, growers would need to directly inject the antibiotic OTC into the tree trunk to reach the phloem of the tree and to adequately control bacterial titer; otherwise, once infected, the citrus tree will become increasingly unproductive and ultimately die. It is currently not recommended for citrus growers to use OTC injections as prophylactics because we do not have much information on how OTC can affect a healthy citrus tree in the field. We also do not know if prophylactic OTC injections can prevent HLB. Nevertheless, when integrating antibiotics into plant disease regimens, knowledge and understanding of the location of the pathogen in the infected plant greatly helps with the efficiency of antibiotic use. Spraying (instead of injecting) OTC to control HLB has proven insufficient and costly for growers (Li et al. 2019; Vincent et al. 2022). Likewise, prevention of antibiotic runoff and residual entrance into the environment further necessitates grower care with applications.

Challenges of antibiotic use in plant agriculture

Using antibiotics in plant agriculture comes with a unique set of challenges. For sprayed antibiotics, the efficiency of applications in agricultural settings is heavily influenced by environmental factors, such as temperature, precipitation, humidity, and ultraviolet radiation. Studies have found that the antibiotic potential of both streptomycin and OTC declines with increased exposure to sunlight (Christiano et al. 2010; Khan et al. 2021). For light-sensitive OTC, degradation in bright conditions can be up to threefold greater than that in dark conditions (Doi and Stoskopf 2000). Similarly, exposure to three consecutive 16-h photoperiods of daily light integrals led to an 80% decrease in formulated kasugamycin (Slack et al. 2021). Artificial rain following streptomycin treatment was also demonstrated to reduce control of fire blight (Luepschen 1960), and as little as 2 min of rain reduced OTC residues on peach leaves by more than 67% (Christiano et al. 2010). Likewise, increased temperatures (43 and 60°C) have been shown to shorten the half-life of OTC, although OTC is one of the more heat-tolerant antibiotics of the tetracycline class (Doi and Stoskopf 2000; Xuan et al. 2010). Such uncontrollable parameters from the environment are particularly important to consider for foliar applications of antibiotics.

In addition to weather, the timing of applications—coupled with knowledge of the pathosystem—is critical for disease management using antibiotics. For example, the findings of Pusey and Curry (2004), and previously those of Thomson and Gouk (2003), showed that populations of *E. amylovora* increase on stigmas before infecting the plant through nectarthodes on the nectary. Apple flowers are susceptible to infection only up to 4 days after opening (Thomson and Gouk 2003). Thus, antibiotics are used to disrupt *E. amylovora* epiphytic growth on the floral stigmas and the nectary, with efficacy dependent on a narrow period of time. Spraying antibiotics after *E. amylovora* migrates into the base of the flower cluster was shown to be ineffective (Cooley et al. 2015). This information—along with disease models (expanded upon in the following section) for pathogen growth on flowers—decreased the number of applications of antibiotics from approximately 20 per year (from the 1950s to about 1980) to zero to four applications annually, depending on the crop, history of disease in the orchard, and weather conditions. Blooming progression can also vary, resulting in nonuniform peak bloom across an orchard (Krikeb et al. 2017; Yoder et al. 2013), which can present an extra obstacle in deciding when to conduct applications. Finally, very few antibiotics have demonstrated sufficient efficacy against plant-pathogenic bacteria in the environment.

For antibiotics injected into the vasculature of plants (specifically OTC in citrus trees), different but equally critical challenges can also occur. Although expanded upon in the section "Application Methods of Antibiotics," trunk injections, for example, will result in wounds and openings of the trunk, along with variation in the uptake and distribution of antibiotics throughout the tree, both key considerations for this type of application (Archer et al. 2023). Moreover, environmental conditions can even influence how quickly antibiotics are circulated during trunk injections (Zamora and Escobar 2000).

On top of the aforementioned obstacles, the strict regulation of antibiotic use in U.S. plant agriculture involves the concern of environmental contamination due to runoff or off-target applications (Almakki et al. 2019; Davis et al. 2006; Nottingham and Messer 2021). Along similar lines, the fear that acquired resistance occurring in plant pathogens may be conferred to animal or human pathogens via horizontal gene transfer (HGT) precedes a scarcity of antibiotics considered for use in plant agriculture and will be discussed more later in the review (Nesme and Simonet 2015; Séveno et al. 2002). It is worth mentioning, though, in the United States, the U.S. Environmental Protection Agency (EPA) conducts an extremely thorough environmental review of all pesticides and their effects on humans and the environment during initial registration, as well as during periodic registration reviews, which will be further expanded upon in the section "Regulations of Antibiotics."

Recent advances in the use of antibiotics in plant agriculture

As shown above, the efficacy of antibiotic treatment is highly sensitive to timing; therefore, several models have been developed to predict the optimal stage for real-time application. Such models have been available to researchers for a few decades, as early as the 1980s (Steiner 1988; Thomson et al. 1982). However, these models are regularly updated and improved upon and evolved in the 1990s as a one-page grower-friendly handout (and associated webpages) that describes how to calculate the risk of fire blight (for instance) using local history of disease, tree phenology, and measured temperatures and forecasts for the next week (Lightner and Steiner 1992; Smith 1999). The latest version of *Maryblyt*, a forecasting program for fire blight in apples and pears, was released in 2015 and included cosmetic and functional changes intended to make the technology more accessible to users (Turechek and Biggs 2015). This technology can help tailor the timing of antibiotic treatments for optimal control, reduce the total number of sprays for disease prevention, and minimize the release of antibiotics into the environment.

The earliest documented use of liquid trunk injections can be traced back to Leonardo da Vinci in the mid-1500s (Roach 1939), but commercial use started around the 1940s to control forest pests such as Dutch elm disease, caused by the fungus *Ophiostoma novo-ulmi* (Haugen and Stennes 1999). Subsequently, liquid trunk injections were used to control diseases in landscape trees, especially lethal yellowing of palms, caused by '*Candidatus* Phytoplasma palmae', starting in the 1970s (Fisher 1975; McCoy 1973). Antibiotic trunk injections have recently gained interest in agricultural settings, especially for citrus in Florida (Archer et al. 2021). This technique was first applied in orchards for fire blight control in the United States (Aćimović et al. 2015), but targeted trunk injections of three formulations of OTC just received emergency approval in 2022 and 2023 in Florida for the treatment of HLB disease in citrus crops (U.S. EPA 2022, 2023a). Together, modeling and trunk injections aim to increase the efficiency of antibiotics. Thus, any future advances should continue to strive for the prolonged efficacy of antibiotic treatments. This may involve integrating additional management techniques into existing models, such as biological controls (Johnson and Stockwell 1998; Johnson et al. 2004), cultural controls to prevent inoculum buildup, and improvement of the labor efficiency of applications.

Presently, in the United States, the EPA has only three antibiotics registered for use—streptomycin, OTC, and kasugamycin (Sundin and Wang 2018)—which stresses the need for vigilance in application efficiency and bacterial population resistance monitoring. Streptomycin in the United States is registered for bacterial disease control on pome fruit (apples and pears), some tree nuts, citrus, some vegetables, and some ornamentals (U.S. EPA 1992). OTC is permitted for use on pome fruit, peaches, nectarines, and coconut palm but was recently approved for a special, local need for trunk injection in Florida citrus to control HLB and will be discussed as a case study below in the section "Application Methods of Antibiotics" (Neff 2022; U.S. EPA 1993). Kasugamycin (as an alternative to streptomycin) is registered for use on pome fruit, cherry, and walnut (Akers 2020). Not much has changed with antibiotics used for U.S. crop production in recent years, with the registration of kasugamycin in 2018 the only major milestone. Additional antibiotics, such as oxolinic acid and gentamicin, are not registered for agricultural use in the United States but have had some success against certain phytobacteria throughout the world, along with incidences of antibiotic resistance, specifically to oxolinic acid (Haynes et al. 2020; Mann et al. 2021; Stockwell and Duffy 2012; Sundin and Wang 2018).

As many as 11 antibiotics have reportedly been recommended for use in plant agriculture in low- and middle-income countries, although they were not approved for crop use in all cases (Taylor and Reeder 2020). Streptomycin and OTC continue to be the most popular and more commonly used antibiotics in crop production. Many of these antibiotics are also considered important to human medicine, according to the World Health Organization (WHO), which makes widespread approval in plant agriculture challenging (FAO and WHO 2018; WHO 2019). Other countries' success with certain antibiotics primarily used in plant agriculture could pave the way for registration in the United States and become rotational partners in our fight against phytopathogenic bacteria. This may ultimately help to delay antibiotic resistance development.

Finally, the development of nano-based pesticide formulations has also been of interest in recent years due to the increased potential to generate products with higher efficacy and safety for the environment (Camara et al. 2019; Kumar et al. 2019). However, there is currently limited research for agricultural antibiotics with nano-formulations. In an experimental setting, kasugamycin was bonded with pectin and enveloped in enzyme-responsive microcapsules, both demonstrating successful release of kasugamycin in the presence of plant-pathogenic bacteria (Fan et al. 2017; Liu et al. 2015). Additionally, metronidazole, an antibiotic not approved for agricultural use, has been encapsulated in a nanogel (Karimi et al. 2017). As the emergence of antibiotic-resistant bacterial populations continues, nanotechnology may soon be at the forefront of producing crop therapeutics that could prevent or slow resistance development.

Antibiotic Resistance Development and Mitigation

The reliance and extensive use of antibiotics in certain agricultural systems have led to unwanted microbial resistance in plant bacteria. Known as antimicrobial resistance (AMR), or specifically antibiotic-resistant bacteria (ARB), cases in crop production can contribute to similar AMR and ARB emergence from human and animal antibiotic overuse. Although AMR naturally exists from the interaction of microorganisms with each other and their environment, human concerns concentrate on ARB development in plant pathogens without prior intrinsic susceptibility to an antibiotic. This section specifically addresses the recent developments of ARB in crop production within the last 10 years, with a focus on the United States (and supplementary worldwide information). We also discuss the significance of effective and sustainable mitigation to prevent and combat antibiotic resistance development in phytopathogenic bacteria.

Antibiotic resistance in phytopathogenic bacteria

Following the registration and use of antibiotics throughout U.S. crop production during the mid- and late 20th century, antibiotics remain a significant and widely accepted method for controlling certain phytopathogenic bacteria (Goodman 1961; Stockwell and Duffy 2012). Products and regulations surrounding their application differ between the United States and other countries, with the incidence of resistance development also variable among regions. Enrichment (or emergence) of bacterial pathogens with resistance to antibiotics can arise from misuse or overexposure and can reduce the effectiveness of antibiotics against these populations (McManus et al. 2002). Although ARB incidence has occurred much less in crop production than in animal agriculture, it can still threaten the efficacy of antibiotics against any major bacterial disease. Additionally, most of the antibiotics used across the United States target phytobacteria of tree crops or high-value crops (NASS-USDA 2017).

Tree crops. The majority of antibiotics currently used in U.S. crop production target bacterial diseases of tree fruit crops, specifically apples, pears, stone fruit, and citrus (Archer et al. 2022, 2023;

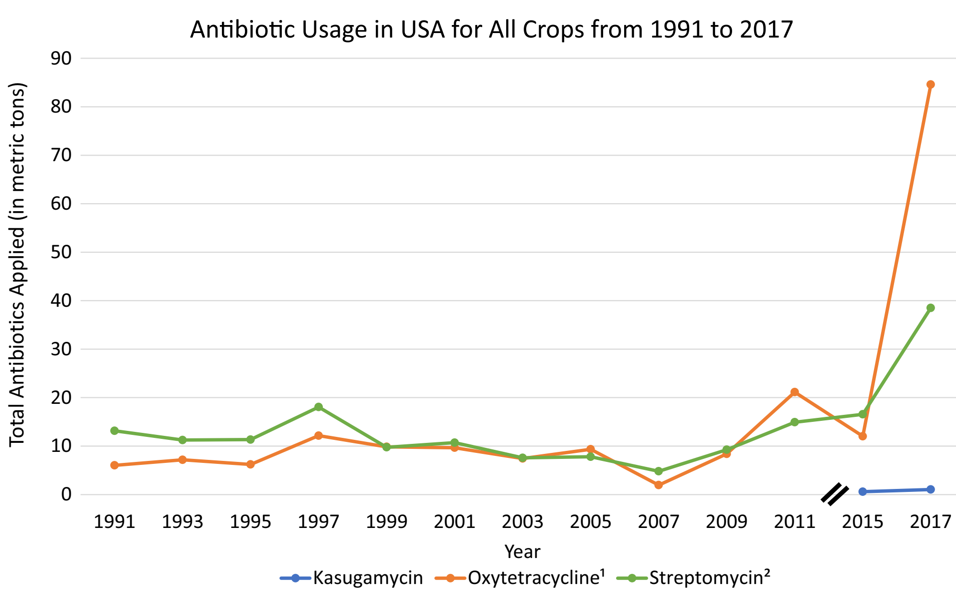
Hu and Wang 2016; Stockwell 2014; Stockwell and Duffy 2012; U.S. CDC 2018). The origin of antibiotic resistance in economically important phytopathogens has always been a subject of concern for the United States, beginning with the emergence of streptomycin-resistant *E. amylovora* (McManus and Stockwell 2001). Fire blight disease has historically been one of the most important bacterial diseases of pome fruit and rosaceous crops and continues to force this sector to depend on streptomycin (and other antibiotics) for adequate control of the disease (Mansfield et al. 2012; Miller et al. 2022; Sundin and Wang 2018; Vidaver 2002). In the United States, streptomycin is predominantly used as a prophylactic for fire blight control, with reduced use against human bacterial diseases (Haynes et al. 2020). The application of streptomycin on *E. amylovora* populations resulted in the emergence of antibiotic resistance genes (ARGs) and resistant populations over the years, as first reported in the early 1970s (Miller and Schroth 1972; Moller et al. 1972). ARGs can be defined as genes that confer resistance to an antibiotic in bacterial populations that were previously susceptible to this antibiotic. Streptomycin was the antibiotic of choice to use during the latter half of the 20th century, applied at almost 40 metric tons of active ingredient between 1991 and 2017 (Fig. 1) (NASS-USDA 2017; Taylor and Reeder 2020). Additionally, OTC and streptomycin sharply increased in 2017, likely as a result of emergency EPA approval for foliar spray use against HLB in Florida citrus (U.S. EPA 2020). In almost every region where streptomycin has been used to control bacterial diseases in the United States, bacterial populations resistant to this antibiotic have been detected (Sundin and Wang 2018) (Fig. 2; Table 1). As a result of the detection of several streptomycin-resistant populations of *E. amylovora*, pome fruit growers began integrating OTC and kasugamycin into their fire blight control (McGhee and Sundin 2011; Stockwell et al. 2008).

Although only three antibiotics are used in the United States, several other antibiotics are employed around the world. Table 1 lists the most agriculturally important antibiotics across the world and countries with detected resistance to these antibiotics within the last 10 years. In the United States, OTC was registered after streptomycin in the 1970s for pear and peach but was not yet registered for apple until the 2000s. As soon as the early 1990s, researchers reported incidences of tetracycline-resistance in tree crop-associated Pseudomonads, Xanthomonads, and *A. tumefaciens* (Luo and Farrand 1999; Spotts and Cervantes 1995). OTC resistance was also just recently reported in additional phytobacteria of tree crops: OTC-resistant *X. arboricola* pv. *pruni* (bacterial spot) populations in South Carolina peach orchards (Herbert et al. 2022) and OTC-resistant *E. amylovora* populations in California pear orchards (Sundin et al. 2023) (Fig. 2). Regardless of OTC use and selection pressure, scientists propose that epiphytic phytobacteria of peach trees naturally harbor and may act as reservoirs of OTC resistance to phytopathogens (Capasso 2016; Herbert et al. 2022). Such studies can remind researchers and growers alike about the additional environmental influences, such as surrounding microbiota, that can exacerbate antibiotic resistance development in major crops.

Although resistance to kasugamycin has not been documented in the United States, researchers in Japan began detecting resistance to this antibiotic in rice pathogens *Burkholderia glumae* and *Acidovorax avenae* subsp. *avenae* over 30 years ago (Fig. 2; Table 1) (Hori et al. 2007; Takeuchi and Tamura 1991; Yoshii et al. 2012). To preserve kasugamycin efficacy, tree fruit growers and researchers should routinely communicate issues and concerns involving this new antibiotic. Similarly, monitoring kasugamycin resistance in phytopathogenic bacteria of crops should also be of consequence.

Other crops. Although AMR and ARB in tree crops remain the priority, growers and researchers have found bacterial pathogens exhibiting antibiotic resistance in other economically important crops. Xanthomonad-associated diseases in solanaceous crops, especially bacterial spot in tomato, have continued to be resistant to streptomycin since detection during the early 1960s in the United States (Rotondo et al. 2022; Stall and Thayer 1962; Thayer and Stall 1961, 1962). Currently, only transplant facilities are permitted to use streptomycin (Strayer-Scherer et al. 2019). Outside the United States, in the Middle East, a genus of soft rot-inducing pathogens of potatoes called *Dickeya* has recently shown resistance to various antibiotics (Soleimani-Delfan et al. 2015). Likewise, Xanthomonads and Pseudomonads infect several economically important crops worldwide, such as kiwi fruit, and resistance to streptomycin was detected multiple times throughout commercial and research settings (Fig. 2) (Cameron and Sarojini 2014). Rice is susceptible to several devastating bacterial infections, such as rice bacterial brown stripe (*A. avenae* subsp. *avenae*), bacterial blight of rice (*X. oryzae* pv. *oryzae*), and bacterial panicle blight of rice (*B. glumae*). As discussed previously, Japan has been detecting kasugamycin resistance of these bacteria since the 1990s (Hori et al. 2007; Takeuchi and Tamura 1991; Yoshii et al. 2012).

FIGURE 1
Antibiotic usage in the United States for all crops during 1991 to 2017. Data from the National Agricultural Statistics Service, USDA 2017. [1] Includes oxytetracycline calcium and/or oxytetracycline chloride formulas. [2] Includes streptomycin sulfate formula. 2013 did not have data.



Resistance in ornamentals and other (wild/cultivated) plants

Antibiotic use in ornamentals and other cultivated/wild plants is substantially less than use in tree crops in the United States (NASS-USDA 2017). Consequently, ARB in ornamentals or other wild/cultivated plants has not been as much of a concern compared with ARB incidence in economically important tree crops. For bacterial pathogens that infect several diverse types of ornamentals, resistance still occurs and can be problematic if antibiotics are not used according to their registered labels.

For example, *E. amylovora* causes fire blight in several ornamental rosaceous crops, such as pyracantha (*Pyracantha* spp.), cotoneaster (*Cotoneaster* spp.), and hawthorn (*Crataegus* spp.) (van der Zwet and Keil 1979; Vidaver 2002). Control for fire blight in some of these plants includes streptomycin and OTC but with fore-

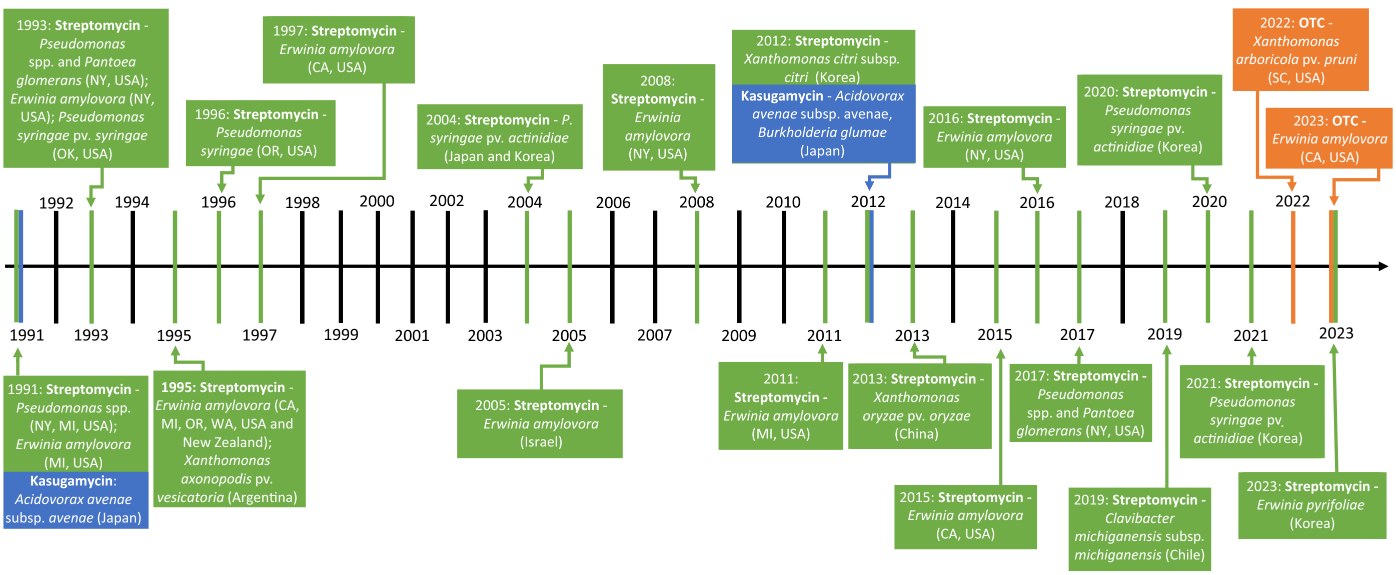


FIGURE 2

Timeline of reported incidences of antibiotic-resistant plant-pathogenic bacteria around the world between 1991 and 2023. Green indicates streptomycin resistance detected; orange represents oxytetracycline (OTC) resistance detected; blue represents kasugamycin resistance detected. Associated references cited (Burr et al. 1993; Chiou and Jones 1991, 1993, 1995; Förster et al. 2015; Han et al. 2004; Herbert et al. 2022; Hyun et al. 2012; Jones et al. 1991; Kleitman et al. 2005; Lee et al. 2020, 2022, 2023; Lyu et al. 2019; McGhee et al. 2011; Norelli et al. 1991; Palmer et al. 1997; Russo et al. 2008; Scheck et al. 1996; Sundin and Bender 1993, 1995; Sundin et al. 2023; Takeuchi and Tamura 1991; Tancos and Cox 2017; Tancos et al. 2016; Valenzuela et al. 2019; Xu et al. 2013; Yoshii et al. 2012).

TABLE 1
List of the most commonly used antibiotics in plant agriculture and regions of with antibiotic resistance detected in plant-pathogenic bacteria roughly within the last 10 years

Antibiotic	Countries with antibiotic use/registration	Crops[a]	Countries with resistance detected (in last 10 years)	Reference(s)
Streptomycin	United States, Argentina, Canada, Chile, China, Iran, Israel, Korea, Mexico, New Zealand	Apples, pears, solanaceous crops, and oranges	United States, Canada, Chile, China, Korea, Mexico	de León Door et al. 2013; Förster et al. 2015; Lee et al. 2020, 2022, 2023; Lyu et al. 2019; Shtienberg et al. 2015; Smits et al. 2014; Soleimani-Delfan et al. 2015; Sundin et al. 2023; Stockwell 2014; Tancos and Cox 2017; Tancos et al. 2016; Valenzuela et al. 2019; Wallis et al. 2021; Xu et al. 2013
Oxytetracycline	United States, Costa Rica, Honduras, Guatemala, El Salvador, Mexico	Citrus, apples, pears, peaches, and palms	United States	Förster et al. 2020; Haynes et al. 2020; Herbert et al. 2022; Rodríguez et al. 2007; Sundin et al. 2023
Kasugamycin	United States, Japan, New Zealand	Apples, walnuts, pears, rice, and cherries	Japan	Yoshii et al. 2012
Oxolinic acid	Israel, Japan, Korea	Apples, pears, and rice	Israel, Japan, Korea	Ham et al. 2022; Kleitman et al. 2005; Shtienberg et al. 2001, 2015
Gentamicin	Mexico, Chile, Costa Rica, Honduras, Guatemala, El Salvador, Thailand	Apples, pears, solanaceous crops, brassica crops	Thailand	Srichamnong et al. 2021; Vidaver 2002

[a] Not exclusive.

warned and expected development of resistance to these antibiotics (Olsen and Young 2011). Additional significant bacterial pathogens, such as *Pseudomonas syringae* pathovars, *Xanthomonas* spp., and *Erwinia* spp., hamper the ornamental and foliage industry but can be successfully controlled by streptomycin formulas (Chase 1986, 1992; Moore 1988). Antibiotic and pesticide applicators should always verify whether the antibiotic can be used on the plant in that region (based on the label). Although antibiotic resistance in these bacteria has not been as economically difficult as *E. amylovora* cases, agricultural extension specialists advise that overuse and application of antibiotics for ornamentals should always be avoided (Chase 1986; Olsen and Young 2011). The higher prevalence of antibiotic resistance in commercial fruit tree crops compared with ornamentals originates from the larger area of production and much larger antibiotic application associated with the fruit crops (Sundin and Wang 2018). When more plants and areas are sprayed with antibiotics on larger scales, chances of detecting resistance during screening can increase.

Resistance in insects

Most documented incidences of antibiotic resistance in agriculture originate from the extensive use of antibiotics in animals of mammalian origin. The animals discussed here include only agriculturally important insects, such as honeybees (apiculture) and silkworms (sericulture). When antibiotics are used on plants for crop production, insect populations that live in or near these agroecosystems can be exposed, potentially at harmful levels (Avila et al. 2022). Additionally, certain antibiotics, such as OTC, are used for insect colonies (in honeybees and silkworms) as therapeutics and to treat lethal bacterial infections (Genersch 2010; Mohanta et al. 2015; Richards et al. 2021). Although most studies focus on antibiotic resistance in medically important human bacterial pathogens, phytopathogenic bacteria of these same genera, such as *Pseudomonas*, *Burkholderia*, and *Streptomyces*, may still be able to acquire transferrable ARGs that persist in this environment (Alippi et al. 2014; Evans 2003; Murray et al. 2007; Resci and Cilia 2023).

Honeybees (*Apis mellifera*), one of the most environmentally important insects, are responsible for pollinating various vital crops and ecosystems worldwide. Like all insects, honeybees harbor a diverse microbiota that can be disrupted by antibiotic use (Li et al. 2017). Specifically, scientists found that honeybee gut microbiota was negatively affected by a mixture of penicillin and streptomycin, and this resulted in a decrease in their immune response and protection against the *Nosema ceranae* microsporidian parasite (Li et al. 2017). When growers spray streptomycin on pome fruit flower blossoms to prevent *E. amylovora* infection, foraging honeybees can be simultaneously exposed, which has incidentally led to the detection of streptomycin-resistant bacteria in U.S. populations of bees (Ludvigsen et al. 2018). These harmful levels of antibiotic exposure not only have the potential to increase ARB within the honeybee gut microbiota but can also negatively impact the insect's behavior and learning (Avila et al. 2022).

Honeybees are particularly susceptible to the gram-positive bacterium *Paenibacillus larvae* and its subsequent larval American foulbrood disease (Evans 2003). Apiculturists have used OTC for more than 50 years to combat *P. larvae*, yet multiple incidences of OTC resistance in the bacteria have weakened the antibiotic as a viable control option (Alippi et al. 2007; Evans 2003; Krongdang et al. 2017; Murray and Aronstein 2006; Tian et al. 2012). Scientists in Canada have recently identified OTC resistance in another bee-infecting bacterium, *Melissococcus plutonius*, the causal agent of European foulbrood disease (Masood et al. 2022). ARGs were likewise detected in bee populations in China (Sun et al. 2022). In a separate study, different ARGs were even detected in honey (S. Li et al. 2021). The presence of ARGs in these environments may facilitate HGT to nearby bacterial populations. Collectively, this research demonstrates the additional threats antibiotic residues in agroecosystems pose and stresses vigilant regulation of their runoff into the environment.

Similarly, the economically important lepidopteran silkworm (*Bombyx mori* L.) has been the basis of sericulture (silk production) in Asia for thousands of years (Cherry 1987). Silkworms can suffer from several debilitating bacterial infections, some of which have been shown to be resistant to antibiotics (Mandal et al. 2022; Mohanta et al. 2015). Spraying insect colonies can also affect the environment and may allow for resistance development in bacteria of the insect via residual buildup.

Resistance mechanisms of phytopathogenic bacteria and mitigation in crop production

The speed at which bacteria can evolve resistance to an antibiotic outpaces the average time it takes the U.S. EPA to approve an antibiotic (Baym et al. 2016; Chahine et al. 2022). Evolution of resistance for plant-pathogenic bacteria versus mammalian bacteria differs, yet some species are closely related and have similar virulence factors, such as the *Enterobacteriaceae* family that contains *E. amylovora*, *Escherichia*, *Yersinia*, and *Salmonella* (Piqué et al. 2015). Prevention or mitigation of antibiotic resistance in populations of *E. amylovora*, for instance, may help to prevent indirect carryover of resistance to closely related bacteria in the environment, such as its relatives that have virulence in humans and animals (Schnabel and Jones 1999). To minimize and/or prevent antibiotic resistance in crop production and subsequent residues, it is important to understand the underlying mechanisms behind this evolution (Piqué et al. 2015; Wang et al. 2011).

According to several decades of extensive research, four overall ways that bacteria can acquire antibiotic resistance include (i) modification of the antibiotic target, (ii) inactivation or ineffectiveness of the drug, (iii) presence and expression of efflux pumps, and (iv) decreased permeability (Blair et al. 2015; Gao et al. 2010; Lavigne et al. 2013; Long et al. 2006; Ogawa et al. 2012). Although these describe the general mechanisms, bacteria have evolved many different ways to resist and overcome antibiotics (Peterson and Kaur 2018). Streptomycin resistance has been shown to occur by a few mechanisms, but mainly (i) inactivation of the streptomycin molecule through gene-encoded enzymes of phosphorylation or adenylation and (ii) spontaneous mutational resistance in the *rrs* or *rpsL* genes, which alters the streptomycin binding site in the bacterial ribosome (Ozaki et al. 1969; Shaw et al. 1993; Sundin and Wang 2018). Mutation of the *rpsL* gene is the most common mechanism of streptomycin resistance; however, early *E. amylovora* strains in Michigan have also acquired resistance with self-transmissible plasmids (Chiou and Jones 1991; Förster et al. 2015; Nischwitz and Dhiman 2013; Tancos et al. 2016). Additionally, the tandem gene pair of *strA/strB*, which encodes for aminoglycoside phosphotransferases that direct phosphorylation and modify streptomycin, is the most common type of streptomycin resistance in the Northeastern United States (Tancos et al. 2016). In terms of recent streptomycin strains detected in Michigan specifically, McGhee et al. (2011) found that *E. amylovora* strain genotypes contained a plasmid with *strA/strB* within transposon *Tn5393*, responsible for the dissemination of streptomycin resistance in Michigan, and that the susceptible and resistant strains in Michigan composed a homogenous population. Thus, these populations are spreading between Michigan orchards and are not independently acquiring these plasmids (McGhee et al. 2011).

OTC resistance in overall bacteria has been documented as (i) efflux proteins or expelling OTC from the cell, (ii) modification of the OTC molecule, (iii) changes to the target site of OTC, and (iv) protection of the cellular OTC targets (Brodersen et al. 2000; Burdett 1993; Guillaume et al. 2004). As mentioned previously, OTC resistance in phytopathogenic bacteria has only recently been detected; specifically, researchers isolated OTC- and streptomycin-resistant *X. arboricola* pv. *pruni* strains from symptomatic fruit in South

Carolina peach orchards (Herbert et al. 2022). Here, OTC resistance was conferred by *tetC* and *tetR* (genes associated with tetracycline-specific efflux pumps), and streptomycin resistance was conferred by the *strA/strB* gene pair (Herbert et al. 2022). The first OTC-resistant *E. amylovora* populations were also recently detected in California carrying a plasmid encoding both streptomycin and tetracycline resistance (Sundin et al. 2023). The *tetB* gene found on this plasmid encoded for a tetracycline efflux ABC transporter, conferring resistance to both OTC and tetracycline; streptomycin resistance in these isolates was similarly conferred by the *strA/strB* gene pair (Sundin et al. 2023). Co-inheritance of OTC and streptomycin resistance often occurs because they are linked to the same mobile genetic element (Schnabel and Jones 1999).

Incidences of kasugamycin resistance have been far less documented, but research from Japan has shown that the bacteria *A. avenae* subsp. *avenae* and *B. glumae* were both conferred resistance by the novel *aac(2')-IIa* gene, possibly acquired via HGT (Yoshii et al. 2012). The *aac(2')-IIa* gene contributes bacterial resistance to kasugamycin by specifically inactivating the target through acetylation (Yoshii et al. 2012).

Maintaining current antibiotic efficacy and reducing dependence. Bacteria are constantly exposed to antagonistic molecules in their environment and have the intrinsic ability to resist these molecules. Bacteria can have this intrinsic antibiotic resistance (resistance independent of HGT and prior antibiotic exposure), have differences in membrane permeability, or acquire antibiotic resistance through HGT or mutations in chromosomal genes (Blair et al. 2015; Fajardo et al. 2008; Jo et al. 2005). A concern of antibiotic resistance in bacteria involves organisms gaining resistance to antibiotics that they would otherwise not be naturally resistant to. For example, McGhee and Sundin (2011) discuss the potential of *E. amylovora* to obtain ARGs from surrounding related bacteria that are intrinsically resistant to kasugamycin. Constant pressure (unregulated antibiotic application) could lead to the selection of nonpathogenic bacteria harboring antibiotic resistance, populating to levels to induce HGT of kasugamycin resistance to nearby *E. amylovora* populations (McGhee and Sundin 2011).

To prevent the emergence of ARB and reduce our reliance on antibiotic use, we need to develop effective alternatives to antibiotics. In agriculture, adopting best management practices can help preserve antibiotic efficacy and reduce our overall dependence on antibiotics. These practices include maintaining crop health and protection, following legally binding methods on the label for antibiotic application and their intended purpose, and monitoring for possible resistance when used.

Managing resistance to antibiotics includes similar approaches for growers managing resistance to other controls, such as insecticides. The less we use antibiotics, the longer their "shelf-life" and efficacy lasts. Mitigation efforts to reduce antibiotic resistance in plant-pathogenic bacteria can include rotational use of pesticides (and antibiotics) and overall sanitation in groves, fields, and orchards, which would reduce overwintering of pathogen populations and possible exposure to antibiotic residues (Stockwell 2014). This is applicable to general plant disease management but can also reduce pathogen pressure and the need for antibiotics. The idea of mixing antibiotics, or "combining therapies," has been proposed as a way to reduce or delay antibiotic resistance in phytobacteria, with some studies showing success against current plant bacterial diseases (Zhang et al. 2011, 2013). However, due to significant uncertainties surrounding the mechanisms of synergism and antagonism between certain antibiotics, there is extreme caution to this approach (Ocampo et al. 2014), but it is allowed for specific plant diseases (Sundin 2019). Apart from chemicals, growers can implement cultural practices to manage avenues of pathogen infection, such as removing blossoms manually or chemically with materials such as lime sulfur (Johnson and Temple 2017) on pome fruit trees to reduce the chances of *E. amylovora* from infecting tissues during high disease pressure. For the long term, breeding for disease resistance in crops susceptible to bacterial diseases remains the priority, however, particularly in tree fruit (Mansfield et al. 2012).

During preparation of this review, the U.S. EPA—in collaboration with the U.S. Department of Health and Human Services and U.S. Department of Agriculture (USDA)—circulated requests for feedback regarding current pesticide use in the agricultural sector (U.S. EPA 2023b). This public request for comment aims to assess whether agricultural antibacterial and antifungal pesticides pose risks to the immediate or long-term effectiveness of human and animal drugs, as well as better ways to conduct these assessments (U.S. EPA 2023b). The current rise in medically important ARB has alarmed not only medical professionals but also policymakers who hope to preserve the efficacy of important antibiotics. This type of collaborative effort can build confidence in our strategies to combat expected resistance development in agriculture and prevent transmission to human bacterial diseases.

Alternatives to antibiotics. Control of certain phytopathogenic bacteria has heavily integrated antibiotics into disease management strategies, most notably streptomycin for fire blight since the 1950s (Stockwell 2014). Consequently, there has been a persistent emergence of streptomycin-resistant *E. amylovora*, leading to the replacement or integration of streptomycin with OTC and kasugamycin in the United States and gentamicin or oxolinic acid in other countries (McManus and Stockwell 2001; Shtienberg et al. 2001). Alternatives to antibiotics, such as biopesticides (biological pesticides), sanitizers, systemic acquired resistance inducers, or essential oils, have less of an impact on environmental and human health and are overall more sustainable choices.

Several biopesticides based on antagonistic microorganisms have been studied and used for effective control over plant-pathogenic bacteria. For control over *E. amylovora*, several United States-registered products include antagonistic fungal and bacterial species, such as Blossom Protect (*Aureobasidium pullulans*), Actinovate (*Streptomyces lydicus*), and Serenade (*Bacillus subtilis*) (Adaskaveg et al. 2006, 2015; Cooley et al. 2015; Gardener and Fravel 2002; Granatstein et al. 2016) (Table 2). The non-exhaustive list of biological, organic, and inorganic alternatives to plant-pathogenic bacteria in Table 2 offers growers environmentally friendly substitutes for antibiotics. Following field trials and evaluations, the products Blossom Protect and Bloomtime Biological seemed to show reliable efficacy in the control of fire blight, yet less control compared with streptomycin (Adaskaveg et al. 2015; Granatstein et al. 2016). Like any pesticide or chemical, it is very important to follow the label and to know if the biopesticide is U.S. EPA-approved for the intended crop and region.

Lime sulfur, copper-based products, and even plant activators such as Actigard (Acibenzolar-S-methyl) have also been used to control plant-pathogenic bacteria in both the United States and other countries (Aćimović and Meredith 2017; Batuman et al. 2022, 2023; Gardener and Fravel 2002; Johnson and Temple 2017; Kunwar et al. 2023a, b; Li et al. 2021b). Copper and sulfur have been historically used against a wide variety of plant pathogens, not only bacteria. However, along with this extensive use, copper resistance in bacterial populations has emerged worldwide, affecting disease management strategies for a number of devastating plant pathosystems (Behlau et al. 2013; S. Zhang et al. 2017). Advanced nano-formulations of copper have recently renewed interest in copper use to control these copper-resistant bacterial populations (Strayer-Scherer et al. 2018; Wang et al. 2013). Although copper-based antimicrobials continue to provide control against certain foliar diseases, its use in trunk injections is currently not advised.

Similarly, sanitizers and essential oils, such as peroxyacetic acid and thyme oil, respectively, show bacteriostatic control over certain bacterial plant pathogens (Behlau et al. 2021; Singh et al. 2017). Furthermore, the use of synthetic or naturally present antimicrobial peptides to induce the plant host defense and directly target

TABLE 2
Non-antibiotic alternative controls used for plant pathogenic bacteria[a]

Type	Active ingredient	Trade name	Bacterial target(s)	Crop(s) used[b]
Biological/ biopesticide	*Aureobasidium pullulans*	Blossom Protect	*Erwinia amylovora*, *Xanthomonas arboricola* pv. *juglandis*	Apple, pear, quince, walnut
	Streptomyces lydicus	Actinovate	*Erwinia* spp., *Xanthomonas perforans, X. axonopodis* pv. *citri*, *X. arboricola* pv. *juglandis*	Various vegetables, herbs, ornamentals (not registered in CA), turf grasses
	Bacillus subtilis	Serenade	*Erwinia* spp., *Xanthomonas* spp.	Various vegetables, cereal grains, fruit tree crops, cotton, grape, herbs, berries
	Bacillus amyloliquefaciens	Double Nickel, Serifel	*Erwinia* spp., *Pseudomonas* spp., *Xanthomonas* spp.	Various vegetables, berries, small fruit, fruit tree crops, grape, ornamentals
	Bacteriophage	AgriPhage	*X. campestris* pv. *vesicatoria*, *P. syringae* pv. *tomato*	Tomato, pepper
	Bacteriophage active against *E. amylovora*	AgriPhage-Fireblight	*E. amylovora*	Apple, pear
Inorganic or salt	Calcium polysulfide	Lime-sulfur solution	*E. amylovora*	Apple, grape
	Copper (Cu)	Various (Previsto, Cuprofix, Phyton 27, Mastercop, Instill, Cueva, Kocide 3000)	*E. amylovora*, *Xanthomonas* spp., *Pseudomonas* spp.	Fruit tree crops, various vegetables, small fruit, vines
	Phosphite (PO_3)	K-Phite 7LP	*E. amylovora*, *Pseudomonas* spp., *Xanthomonas* spp., *Clavibacter* spp.	Brassica crops, cereal crops, pome fruit, cucurbits
	Copper and lime	Bordeaux mixture	*E. amylovora*, *Xanthomonas* spp., *Pseudomonas* spp.	Fruit and nut tree crops, vines, ornamentals
PGR/SAR	Acibenzolar-S-methyl	Actigard	*E. amylovora*, *Xanthomonas* spp., *Pseudomonas* spp.	Various vegetables (leafy), pome fruit, berries
	Prohexadione calcium	Apogee	*E. amylovora*	Apple, pear, peanut
	Yeast extract hydrolysate from *Saccharomyces cerevisiae*	KeyPlex 350	*Pseudomonas* spp.	Various vegetables, fruit tree crops, tree nuts, cotton
	Chitosan	Elexa 4	*Pseudomonas* spp.	Various vegetables, tree fruit crops, cereals/grains
Sanitizer	Hydrogen peroxide	Jet-Ag, OxiDate 2.0	*Erwinia* spp., *Pseudomonas* spp., *Xanthomonas* spp.	Various vegetables, fruit tree crops, tree nuts, fruit, cut flowers, turf/sod
	Peroxyacetic acid	Perasan A	*Erwinia* spp., *Pseudomonas* spp., *Corynebacterium* spp., *Xanthomonas* spp.	Various root vegetables, tree fruit crops, cereals, nuts, cotton, coffee
Essential/natural oil or product	Cinnamon oil	Cinnerate	*Xanthomonas* spp.	Cucurbits, brassica, solanaceous, various vegetables and herbs, fruit and nut trees
	Thyme oil	Thyme Guard, Thymox	*Pseudomonas* spp., *Xanthomonas* spp.	Cucurbits, tomato, citrus
	Tea tree oil	Timorex Act	*Xanthomonas* spp., *Pseudomonas* spp., *Erwinia* spp.	Berries, fruit tree crops, cereal crops, various fruit and vegetables
	Natural oil blend (rosemary oil, clove oil, thyme oil, wintergreen oil)	Sporatec	*Xanthomonas* spp., *Pseudomonas* spp.	Berries, various fruits and vegetables, fruit and nut tree crops
	Citric acid	Procidic	*Corynebacterium insidiosum*, *Agrobacterium tumefaciens*, *Erwinia* spp., *Xanthomonas* spp., *Burkholderia glumae*	Vegetables, tree nut crops, stone fruit crops, berries, cut flowers, vines

[a] Not an exhaustive list. PGR, plant growth regulator; SAR, systemic acquired resistance.
[b] Always verify that the product is legally allowed for use on the crop in accordance with the label and the U.S. Environmental Protection Agency.

phytobacteria has demonstrated effective control, especially with Xanthomonads (Datta et al. 2015; Shi et al. 2016). Antimicrobial peptides have broad-spectrum capabilities (targeting bacteria, fungi, and viruses) and have been isolated from various environments, such as insects and plants (Shi et al. 2016). Their environmental sustainability and efficacy for phytobacterial disease control can expand management options available to growers and help to decrease our overall dependence on antibiotics.

Although not as widely used in biological controls, bacteriophages of plant-pathogenic bacteria are of interest and have been researched extensively in the past decade. Specifically, for *E. amylovora* (Born et al. 2017; Gdanetz et al. 2024) and bacterial blights and rots caused by *Pseudomonas* spp., *Pectobacterium* spp., and *Dickeya* spp. (Czajkowski et al. 2014, 2015; Rombouts et al. 2016), phages have offered promising potential to control their bacterial host counterparts. Like antibiotics, most of the control measures used for plant-pathogenic bacteria may eventually select for resistance, but the goal is to regulate and restrict the use of such products to prevent this from occurring or to at least slow resistance development.

From an economic perspective, fruit trees face the greatest bacterial threats due to high expenses associated with crop production, as well as extended generation times that delay resistance breeding. Plant breeders have focused heavily on fire blight resistance breeding in pear, apple, and other pome fruit because of the destructive bacterial epidemics for growers worldwide (Kellerhals et al. 2017; Peil et al. 2021). Although the long-term solution to control these pathogens is resistance breeding, sustainable control with these resistant varieties can take longer than most growers have and hinder us in the arms race against these microorganisms. Until resistant varieties show long-term defense against these pathogens, short-term controls must be strictly regulated to reduce the chances of microbial resistance.

In conclusion, the emergence of AMR and ARB will persist regardless of human behavior and agricultural practices. However, a critical point to consider is that human actions may accelerate the selection of resistance in bacterial plant pathogens. As stressed previously, certain phytopathogenic bacterial pathosystems heavily rely on antibiotics, yet increased integration of other non-antibiotic controls (and integrated pest management strategies) can extend the antibiotics' efficacy and decrease our considerable reliance on them. ARB is an ongoing threat to humans medicinally and agriculturally, and non-antibiotic replacements and integrative measures can help with the fight against ARB.

Regulation of Antibiotics

The growing popularity of antibiotics in crop production has increased our need for more robust oversight and global regulations. Aside from the three most popular antibiotics in the United States, streptomycin, OTC, and kasugamycin, respectively (McManus 2014; T. Zhang et al. 2017), other antibiotics used outside the United States include gentamicin (McManus et al. 2002) and zhongshengmycin, which is the most recommended in China (T. Zhang et al. 2017). Additional antibiotics restricted to agricultural settings around the world include ningnanmycin, validamycin, aureofungin, and oxolinic acid (Shtienberg et al. 2001; Taylor and Reeder 2020). The following section will discuss both domestic and international regulations associated with these antibiotics in plant agriculture, as well as the necessity for worldwide monitoring associated with their use.

Antibiotic regulations in the United States

In the United States, antibiotic use on crops and ornamental plants is regulated by the EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (U.S. EPA 2012). EPA regulatory decisions extend beyond the efficacy of disease control and include evaluation of the potential impact of the chemicals on human health and the environment. The EPA assesses the potential development of antibiotic resistance and requires specific studies based on the active ingredients, qualitative analyses, and consultations with the U.S. Food and Drug Administration, Centers for Disease Control and Prevention, and USDA. The registration process of the EPA requires strict toxicity and carcinogenicity evaluation of the antimicrobial product and knowledge regarding any impacts that the chemical may have on nontarget species such as aquatic organisms, insects, plants, and general wildlife, as well as a cost-benefit analysis. The registration of antibiotic pesticides sometimes requires submitting monitoring data, and time-limited registrations may be issued, particularly if resistance issues are not immediately known after applications (U.S. EPA 2012, 2023c). Antibiotics are registered for specific crops, mostly for tree fruit: apple, citrus, pear, peach, and nectarine. Their use is prohibited in corn, rice, fibers, grains, grapes, and berries (U.S. EPA 2012). For certified organic farms, antibiotics have only been permitted for use in pear and apple production to control the bacterial disease fire blight until it was prohibited by the National Organic Standards Board in 2014 (USDA 2023). For citrus in the United States, the EPA currently has emergency approval for trunk injections of OTC in Florida groves affected by HLB (U.S. EPA 2022, 2023a).

Antibiotic regulations outside the United States

Regulations pertaining to antibiotics on plants differ significantly across countries and regions worldwide, with many gaps in data and reports. The European Union (EU), the United Kingdom, and Brazil currently prohibit antibiotics as active ingredients in pesticides (Donley 2019). Several EU states and the United Kingdom have used antibiotics historically to control diseases in vegetable, fruit, or ornamental crops, but this has been discontinued (European Commission, Directorate-General XXIV Consumer Policy and Consumer Health Protection 1999; European Commission, Directorate-General for Health and Food Safety 2019; Young et al. 1999). In many high-income countries, the use of antibiotics on crops is prohibited or regulated but can be permitted for emergency situations in specific crops to control outbreaks. When such use is permitted, it is usually in negligible volumes, and the application is strictly controlled, but occasionally, the use can be widescale (European Commission Directorate-General for Healthy and Food Safety 2019; Stockwell and Duffy 2012; Taylor and Reeder 2020). Many other countries do not have laws pertaining to antibiotic use or have some degree of regulation, with some conflicting usage recommendations between different organizations within those countries (Khullar et al. 2019).

A joint investigation by the Food and Agriculture Organization (FAO), World Organization for Animal Health, and WHO concerning AMR found that few countries monitor the use of antibiotics in plant agriculture compared with the monitoring of antibiotics in the veterinary and medical sectors (FAO and WHO 2018). The study included 194 WHO Member States, 40 of which did not respond to surveys. Only 3% of the 194 countries acknowledged regular assessments of the specifics on their antibiotic uses in terms of type and amounts. This is much lower than the monitoring systems in place for human and animal use, 26 and 23%, respectively (FAO and WHO 2018), although this number is also low. A large majority (83%) of the countries surveyed indicated that they lacked the ability to monitor antimicrobial use on plants or did not respond. Systems for monitoring the use of antimicrobials in the plant sector exist only in 11 high-income countries and three upper-middle-income countries (FAO and WHO 2018). Seventy-eight of the 194 countries have regulations to prevent environmental contamination issues, but only 10 of them have the full systems in place to ensure regulatory compliance for waste management, including limiting the discharge of antimicrobial residues. The study highlighted the concern that substantial data are missing from the environmental and plant sectors, and progress is only being achieved on animal antibiotic use data (FAO and WHO 2018).

A CABI Agriculture and Bioscience study, focused on analyzing antibiotic use in a group of low- and middle-income countries (LMICs), found that four of the six WHO regions, the Americas, Southeast Asia, East Mediterranean, and Western Pacific, use antibiotics in crop production, with no official use in Africa and not enough information on Europe (Taylor and Reeder 2020). In many LMICs, including in Africa, antibiotics are readily accessible through unregulated markets and over-the-counter sales (Taylor and Reeder 2020), despite the lack of official crop application reports. In China, the use of antibiotics for crop production is higher than reported, even as 4.5% of crop advisors are known to promote antibiotic use, which is often supported by government subsidies (Taylor and Reeder 2020; T. Zhang et al. 2017).

There are international programs, such as Plantwise, that assist in providing agronomic recommendations that may have regulatory implications, and they primarily target smallholder farmers in LMICs (Taylor and Reeder 2020). The Plantwise Online Management System database contains data that describe which plant health problems farmers seek help for in individual countries, and it helps assess the levels of antibiotic use in these countries where there is a lack of monitoring and regulating antibiotic use (Taylor and Reeder 2020). There are estimates that the overall antibiotic use in agriculture ranges between 57,000 and 217,000 metric tons per year (O'Neill 2015), but it is unknown what percentage of this is in crops. In the United States, the antibiotics applied to plants are less than 0.5% of the total antibiotic use as well (McManus and Stockwell 2000), but there have been specific crop emergency situations in which this was greatly inflated. One example of this was the EPA allowing the use of approximately 265,000 kg of streptomycin per year since the devastating outbreak of HLB in the United States. Since 2018, the U.S. EPA has approved antibiotic use on roughly 194,000 ha of citrus trees with approximately 176,000 kg of OTC per year. Following emergency U.S. EPA approval, the use of OTC on citrus crops increased yearly, equal to approximately 59,000 kg more than all tetracycline used in human medicine in the United States.

The One Health approach for globally preventing AMR. The FAO and WHO jointly maintain a "Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance," which was started in 2005 and recently amended in 2021 (FAO and WHO 2021). This guideline provides information pertaining to risk management advice for ensuring responsible and prudent use of antimicrobials and is specifically focused on addressing risk to human health. It discusses different aspects of antimicrobial risks throughout the food chain process from production to consumption. Here, primary production encompasses the crop and plant aspect of antimicrobial usage.

The key principles of this guideline emphasize the focus on containing practices to embody the One Health approach that address antimicrobial risk management (FAO and WHO 2021). It defines the One Health approach as a collaborative, multisectoral, and transdisciplinary approach that works toward a goal of achieving optimal health outcomes and recognizes the interconnection between humans, animals, plants/crops, and their shared environment. One of the most common rules mentioned in this guideline is the importance of utilizing plant/crop health professionals as a major resource when making decisions involving antimicrobial use, and developing risk assessments and strategies (FAO and WHO 2021). Everyone involved in the primary production of food must always follow available national legislation pertaining to antimicrobial usage. Producers cannot use antimicrobials as a replacement for good management and farm hygiene.

Integrated pest management is an integral part of antimicrobial usage decisions. This must include consultation with a plant/crop health professional, historical and epidemiological knowledge of the disease and pest issue at hand, and vigilance for the status of the issue. Growers must use only authorized products according to their labels, and alternatives to antimicrobials and their safety and efficacy should be considered if they exist for the specific issue. Some important facets of labels include using the antimicrobial product for the intended species at approved doses, correct storage conditions, recommended withdrawal periods and preharvest intervals, disposing of outdated product, and keeping detailed records of all antimicrobial agents used. Additionally, although medically important antimicrobials are sometimes permitted in certain circumstances in a veterinary setting, they should not be used off-label for plants/crops except for specifically legislated emerging disease control.

The manufacturers and marketers of antimicrobials also have a responsibility and role to play in helping maintain safe practices. The marketers must supply all information that can help establish the quality, safety, and efficacy of the products and ensure that this information was obtained through appropriate procedures, tests, and trials. Although there are comprehensive and thorough guidelines focused on maintaining human health regarding antimicrobials, it could be beneficial to include an additional focus on their impacts on the environment and wildlife.

Further regulations needed

Multiple studies highlight the insufficient data and regulatory framework concerning antibiotic usage in many parts of the world. Although some countries exhibit transparency with well-defined guidelines and oversight from government agencies, the majority do not have a regulatory infrastructure in place dedicated to monitoring or enforcing antibiotic use in the plant agriculture context, in contrast to the stricter regulations in the human and animal sectors. In a globalized market, where plant products are shipped around the entire world, it is imperative to increase awareness and manage data on antibiotic use. It is also important to regularly update antibiotic regulations for possible consumer health implications, antibiotic resistance issues, and maintenance of market transparency. This can ultimately help construct the best antibiotic usage guidelines with which to advise countries.

Application Methods of Antibiotics

The success and efficiency of the antimicrobial compounds rely on how well they can reach target areas. This, in turn, also depends on the timing and the method of antibiotic application. Antibiotics are mostly applied using foliar or airblast sprays in orchards (Vidaver 2002), as well as trunk injection, which is used in landscapes and high-value fruit crops, including—most recently—Florida citrus (Aćimović et al. 2015; Amanifar et al. 2016; Archer et al. 2022, 2023; Cooley et al. 1992; Harrison and Elliott 2008; Hu and Wang 2016; Reil 1979; Rumbos 1986; Shin et al. 2016). This section will explore the pros and cons of legalized and popular antibiotic application methods and highlight our attempts to adopt antibiotic use for controlling HLB disease in citrus groves in Florida.

Foliar and airblast sprays

Foliar spray or airblast treatment is one of the most popular methods for applying antibiotics in orchards (Vidaver 2002). In commercial orchards and groves, antibiotic powders are usually mixed in a large volume of water, from 50 to 200 parts per million (ppm), and are subsequently blown into tree canopies with a high-pressure (airblast) sprayer pulled by a tractor (Haynes et al. 2020). Depending on the crop type and area, some growers use CO_2-powered handheld or aircraft sprayers.

Foliar sprays or airblast treatments of streptomycin and OTC have been registered to manage several economically important phytopathogens in tree crops, such as fire blight of apples and pears and bacterial spot of peaches (Table 3). Kasugamycin spray can manage walnut blight in walnut and bacterial blast and canker in cherries (Table 3). Streptomycin is also registered to treat bacterial blights, bacterial spots, and specks in annual crops, such as beans, celery, pepper, tomato, and potato (Table 3). Importantly, the treatment of annual crops with streptomycin is permitted in greenhouses prior to transplanting, but application in fields is not permitted. Florida citrus growers were applying streptomycin and OTC sprays early on during attempts to control HLB under the emergency exemption of the United States Federal Insecticide, Fungicide, and Rodenticide Act (section 18C) (Haynes et al. 2020).

Factors affecting efficiency of foliar spray and airblast treatments. In general, the intake of sprayed agrochemicals by plants depends on several considerations, such as plant type, plant canopy size and density, type of antibiotic used, time of year and weather conditions (wind speed and direction) during application, the condition of the leaf surface (the waxy cuticle), and the adjuvant and the sprayer used (Bondada et al. 2006; Killiny et al. 2020; Orbović et al. 2001; Vincent et al. 2022). Below, we expand upon the key factors affecting the efficacy of foliar antibiotic sprays.

Timing of application. A spray treatment of streptomycin (every 3 to 4 days) and OTC (4 to 6 days) is applied as a preventive measure to limit fire blight damage in pome fruit but is only effective if sprayed during flowering (McManus and Stockwell 2000). When *E. amylovora* migrates internally from the floral tissue into stems and branches, causing diagnostic wilting and dieback, an-

TABLE 3
Major bacterial plant diseases and pathogens of vegetables and fruit trees that are managed using air blast (foliar) spray application of antibiotics in the United States

Antibiotic/crop	Disease	Pathogen	Label
Oxytetracycline hydrochloride (trade name: FIRELINE 17 WP; Group 41 Fungicide/Bactericide)			https://www3.epa.gov/pesticides/chem_search/ppls/080990-00001-20190509.pdf
Pears	Fire blight	*Erwinia amylovora*	
Apples	Fire blight	*E. amylovora*	
Peaches and nectarines	Bacterial spot	*Xanthomonas campestris* pv. *pruni* (*X. arboricola*)	
Citrus crop group	Huanglongbing/citrus greening	'*Candidatus* Liberibacter asiaticus'	
Citrus crop group	Citrus canker	*X. citri* pv. *citri*	
Oxytetracycline calcium (trade name: Mycoshield; Group 41 Fungicide/Bactericide)			https://www.cdms.net/ldat/ld246000.pdf
Pears	Fire blight	*E. amylovora*	
Apples	Fire blight	*E. amylovora*	
Peaches and nectarines	Bacterial spot	*X. campestris* pv. *pruni* (*X. arborícola*)	
Citrus crop group	Huanglongbing/citrus greening	'*Candidatus* Liberibacter asiaticus'	
Citrus crop group	Citrus canker	*X. citri* pv. *citri*	
Streptomycin (trade name: Agri-Mycin 17; Group 25 Agricultural Streptomycin)			https://www3.epa.gov/pesticides/chem_search/ppls/055146-00096-20150805.pdf
Pears: (note that rate changes regarding California)	Fire blight	*E. amylovora*	
Apples	Fire blight	*E. amylovora*	
Celery (Florida)	Bacterial blight	*Pseudomonas syringae* pv. *apii*	
Pepper (transplants)	Bacterial spot bacterial speck	*X. campestris* pv. *vesicatoria*, *P. syringae* pv. *syringae*	
Tomato (transplants)	Bacterial spot bacterial speck	*X. campestris* pv. *vesicatoria*, *P. syringae* pv. *syringae*	
Kasugamycin hydrochloride hydrate (trade name: KASUMIN 2L; Group 24 Aminoglycoside Antibiotic Fungicide; liquid formulation comprised of 2% kasugamycin [by weight] as the active ingredient)			https://www3.epa.gov/pesticides/chem_search/ppls/066330-00404-20191021.pdf
Bearing and non-bearing cherry	Bacterial blast	*P. syringae* pv. *syringae*	
Bearing and non-bearing cherry	Bacterial canker	*P. syringae* pv. *syringae*	
Bearing and non-bearing pome fruit (apple and pear)	Fire blight	*E. amylovora*	
Bearing and non-bearing walnut	Walnut blight	*X. campestris* pv. *juglandis*	

tibiotic treatments are not effective. For preventing bacterial spots (*X. arboricola*) in peaches and nectarines, OTC is applied at 5- to 7-day intervals when the disease pressure is at its maximum (McManus and Stockwell 2000). Similarly, to successfully manage bacterial spot of stone fruits such as apricots, plums, and cherries, foliar sprays must be applied preventively when fruits are most susceptible.

Temperature. The efficacy of antibiotic sprays is also influenced by temperature. Most bacterial pathogens grow more quickly in warmer temperatures; therefore, spraying may not be necessary if the temperature is expected to be too low. For example, spraying in apples and pears is not needed for fire blight management if temperatures during flowering are too low for high pathogen populations to develop (McManus and Stockwell 2000). In places such as the United States, appropriate use of disease risk models has greatly decreased the frequency and volume of antibiotics sprayed on the crops. Previous reports have also demonstrated that the increase in temperature increases uptake through the leaf cuticle, thereby improving application efficacy (Orbović et al. 2001).

Humidity. Research suggests that hydration or relative humidity increases the penetration of chemicals in the leaves (Orbović et al. 2001). Al-Rimawi et al. (2019) demonstrated that the amount of OTC in leaves soaked in OTC solution (200 µg/ml) for 3 days was relatively higher than in those treated with the foliar application, indicating how the increase in relative humidity of the citrus plant surface could increase the uptake of OTC.

Adaxial versus abaxial spray. The abaxial leaf surface (lower side of a leaf) has been shown to be more porous or permeable than the adaxial leaf surface (upper side), possibly from the higher abundance of stomata present on the lower side. Orbović et al. (2007) showed that the uptake of a copper-based fungicide was substantially enhanced through the isolated abaxial citrus leaf cuticle after adding a silicone-based surfactant. Conversely, there was no noticeable change in the uptake of copper fungicide through the adaxial leaf cuticle, which lacks stomata. Furthermore, previous reports demonstrated that the citrus leaf adaxial side is covered by a thick lipidized cuticle consisting of hydrocarbons, primary alcohols, and fatty acids, an additional barrier to foliar uptake from the adaxial side (Etxeberria et al. 2016; Killiny et al. 2020). Research has demonstrated that the uptake of foliar-applied OTC was also enhanced by the perforation of the citrus leaf cuticle, suggesting that the citrus leaf cuticle acted as the main barrier against the uptake of OTC (Killiny et al. 2020).

Leaf cuticle. Etxeberria et al. (2016) and Killiny et al. (2020) showed that the citrus leaf cuticle can function as an impenetrable barrier to any influx of foliar-applied compounds. The results from Killiny et al. (2020), including transmission electron microscopy, suggested that intact citrus leaves absorbed only trace amounts of OTC due to the presence of a thick (0.5 to 1.8 µm), uniform, and compact cuticle with no stomata, creating a physical obstruction to chemical intake.

Researchers have found ways to improve chemical penetration via cuticle, including dewaxing leaves and laser light. Bondada et al. (2006) showed that dewaxing the cuticles of citrus leaves significantly increased the total penetration of urea through isolated citrus cuticles by 64%. Similarly, perforation of citrus leaf cuticles with laser light was found to be effective in enhancing OTC uptake and reducing *C*Las titer in the greenhouse and field experiments (Killiny et al. 2020).

Adjuvants affect chemical uptake via leaves. Adjuvants are tank additives that increase the coverage and retention of sprays while also correcting any issues with pH. Multiple research laboratories are working on developing efficient adjuvants that help to improve rain fastness, ultraviolet stability, vascular mobility, and sustained release of antibiotics. Maxwell et al. (2020) reported that the efficacy of these is largely affected by the type of applied antibiotics, selected adjuvant, and plant species. For example, Vincent et al. (2022) and Killiny et al. (2020) evaluated several adjuvants' impact on the uptake of OTC and streptomycin, applied as a foliar spray, in citrus plants and found extremely low levels of both antibiotics in leaves, indicating that neither of the antibiotics was systemically delivered by the foliar application even after being mixed with adjuvants. A proper evaluation of antibiotics and adjuvant tank mix for each host-pathogen system is therefore crucial.

Nozzle droplets. Several studies are currently being investigated to optimize airblast sprayers through nozzle changes or air assistance to improve spray deposition into the canopy while minimizing chemical drift (McCoy et al. 2022).

Limitations of foliar spray

Foliar spray often leads to substantial chemical losses due to atmospheric drift and can affect nontarget organisms. Similarly, it provides limited coverage in large fruit trees. Pimentel (1995) reported that only 0.4% of active chemical reaches the target pest during foliar application. Electrostatic sprayers can also be an option for increasing the effectiveness of treatments and reducing pesticide use due to their high deposition rate and low drift properties. However, in a recent study, the appropriate design of orchard sprayers according to the canopy structure was found to be more effective than the implementation of a charging system (Salcedo et al. 2023). A number of variable-rate technologies have been developed in an effort to increase the efficiency of air blast applications in orchard settings, including pulse width modulation, pressure-based, and variable concentration systems (Wei et al. 2023). A prototype of the pulse width modulation variable-rate spray system has been shown to decrease off-target application within a research plot during foliar sprays by as much as 90% and in some cases reduce drift to undetectable levels (Chen et al. 2013). Furthermore, this technology was then retrofitted so that it could be adapted to growers' existing spray equipment. At a commercial apple orchard, the total spray volume applied using a retrofitted variable-rate sprayer was less than half the volume of the grower's standard application (Fessler et al. 2020). The benefits of these reductions are twofold: reducing the cost of application and decreasing environmental contamination, which could be particularly vital in antibiotic applications that limit pressure for resistance development. Although this technology has been shown to successfully control fungal diseases and insect pressure on multiple fruit crops (Chen et al. 2020), further investigation into using this technology to treat bacterial pathogens is needed. As mentioned in previous sections, timing is also critical for the success of the foliar applications. For example, in the case of diseases such as fire blight of pome fruit, little or no benefit was seen if antibiotics were sprayed after the bloom period. Foliar antibiotic sprays are only effective against exposed populations of the bacterial pathogen on plant surfaces prior to infection.

Foliar spray is generally less effective than trunk injection in targeting phloem-limited pathogens because the antibiotic has to move through the plant's vascular system before reaching the pathogen residing in the infected area (deBoer and Satchivi 2014; Li et al. 2019, 2021a). Published studies indicated better reduction in *C*Las titers in citrus trees and better HLB disease control using trunk injection compared with foliar sprays (Archer et al. 2022, 2023; Bondada et al. 2006; Hu and Wang 2016; Killiny et al. 2020; Vincent et al. 2022). Ultimately, foliar spraying is the most preferable and common way of applying pesticides to trees due to ease of application, although its overall efficiency decreases due to drift and the physiological location of target organisms. Spraying large trees is often difficult, and some states have banned spraying pesticides near urban areas (Aćimović et al. 2016; Wise et al. 2014).

Trunk injection

Trunk injection is a highly precise and environmentally friendly method for delivering chemicals and nutrients directly to the plant's vasculature (Guillot and Bory 1999; Hillebrand et al. 1998; Wise et al. 2014). In the last 20 years, the practice of injecting chemicals directly into tree trunks has become more popular due to advancements in injectable formulations and equipment (Archer and Albrecht 2023; Berger and Laurent 2019; Doccola and Wild 2012). Such technology has simplified the injection process and increased efficiency (Dal Maso et al. 2014; Doccola et al. 2003; Montecchio 2013; Ojo et al. 2024a; Takai et al. 2003, 2004).

Published research has consistently demonstrated the efficacy of trunk injection of antibiotics for managing bacterial diseases in several fruit and landscape trees (Table 4). For example, trunk-injected OTC has been shown to manage HLB in citrus, almond leaf scorch (*Xylella fastidiosa*) in almonds, mycoplasma infections in apricots, and phytoplasma infections causing lethal bronzing of palms (Table 4). Both OTC and streptomycin are also effective against apple fire blight when trunk injected (Table 4). In October 2022, a label was approved under the Federal Insecticide, Fungicide, and Rodenticide Act section 24(c) that allows injecting OTC into mature citrus trees in Florida and has been used widely against HLB disease since the early 2023 growing season (O. Batuman, *personal observations*; Neff 2022). Indeed, in our studies conducted in 2020 to 2022, mature 'Valencia' and 'Hamlin' sweet orange (*Citrus sinensis*) and 'Duncan' grapefruit (*C. paradisi*) trees were trunk injected with OTC in the spring and/or fall to evaluate the effects of injection timing and response to the injection (Archer et al. 2023). In these studies, OTC-injected trees showed a significant reduction in visible symptoms, bacterial titers, and fruit drop, which significantly increased fruit quality, size, and yield (Archer et al. 2023), and the results were consistent with previous results reported by Hu and Wang (2016) and Hu et al. (2018). Specifically, the timing between OTC injection and fruit harvest was 123 days for Valencia oranges, 68 days for Duncan grapefruits, and 32 days for Hamlin oranges (Archer et al. 2023). In particular, Duncan grapefruit trees, despite not being treated again in the next season, sustained improved tree health the following year after the conclusion of these studies (O. Batuman, *personal observations*).

Advantages of trunk injection compared with foliar sprays. There are several benefits to using trunk injection as a way of managing plant-pathogenic bacteria relative to foliar sprays. First, they can eliminate chemical loss due to spray drift (Berger and Laurent 2019). Second, they offer precise delivery and allow for a higher concentration in the plant tissue, thus requiring fewer applications (Vincent et al. 2022). Additionally, they can reduce risks for non-target organisms and worker contact with materials, thus causing less concern for human health and the environment. Finally, antibiotics administered directly into plant tissue are less likely to be removed by rain or degraded by sunlight, resulting in more stability and extended residual activity of the antibiotic.

Trunk injection devices and technologies. There are diverse methods available for delivering liquid materials into tree trunks (Ojo et al. 2024b). Most require drilling a large hole and injecting the desired material using high pressure. The injection systems are most commonly classified as macro-injection, micro-injection, and direct injection based on the pressure apparatus, the diameter, and depth of the injection port, as well as the drill bit.

Macro-injection. With macro-injections, a large volume of chemicals, up to 189 liters in very large trees, can be injected under gravity or pressure for long-term protection (Li and Nangong 2022). Doccola et al. (2007) demonstrated that high-volume macro-injection treatments could last up to 3 years. Typically, macro-injection diameters are 9.53 mm or more with depths of 2.54 mm or more (Costonis 1981). Macro-injections have been used in several published reports to manage nutritional deficiency and fungal diseases such as anthracnose (*Discula* spp.), oak wilt (*Bretziella fagacearum*), Dutch elm disease (*Ophiostoma novo-ulmi*), and iron deficiency chlorosis (Martínez-Trinidad et al. 2009; Stipes 2000).

Micro-injection. Micro-injection uses a small volume of solvent (2 to 30 ml) to inject the active ingredient (Li and Nangong 2022). Micro-injection diameters are typically 4.76 mm or less, with depths of 19.05 mm or less (Costonis 1981). The micro-injection equipment typically consists of an injection gun, a drill, and other smaller tools. There are two methods of micro-injection systems: low pressure and high pressure. High-pressure injection systems, such as Arborjet Quik-jet Air (Arborjet, Woburn, MA), can quickly inject substantial amounts of product into a tree. However, this method also increases the tree's risk of girdling and damage (Archer et al. 2022; Shang et al. 2009). Low-pressure systems, which include a syringe or needle-based methods, such as Chemjet (Kerrville, TX), FlexInject (TJ Biotech, LLC, Buffalo, SD), Rainbow Treecare (Minnetonka, MN), and Mauget (Arcadia, CA), use lower pressures (<60 psi) and have smaller injection port sizes, which allow for quicker wound repair (Archer et al. 2022; Martin and Dabek 1985).

No-pressure systems, such as the Acecap (Creative Sales, Fremont, NE), use active components and consist of capsules inserted into a drilled hole mobilized into the tree with passive infusion (Archer et al. 2022). The liquid passively flows into the tree with the xylem sap's transpiration pull. Unfortunately, this passive process can take several hours for the trees to uptake. No-pressure systems tend to be slower and might not evenly distribute materials, which could also reduce the amount of material that can be applied quickly.

Critical factors and limitations of trunk injection

Some of the factors that determine the efficiency of agrochemical injection into trees include the following:

1. The need for specialized equipment and training: The trunk injection method can be more complex than other control options.
2. Associated cost and labor: Trunk injection can be costly and require large initial investments (see section "Economics of Antibiotics" below).
3. Tree damage from wounding: Trunk injection technologies are often criticized for their potential to injure trees and impede wound healing (Berger and Laurent 2019). However, there is limited information on the most effective approach for performing trunk injections commercially and the extent of damage inflicted. In a recent study, it was shown that OTC injection caused external and internal damage but significantly improved tree health, whereas imidacloprid (insecticide) injection caused less damage yet did not provide lasting benefits (Archer and Albrecht 2023; Archer et al. 2022). The study suggested that the benefit gained by tree injection may sometimes outweigh the risk of wounding caused by the treatment.
4. Phytotoxicity concerns: Some antibiotics, such as OTC, are toxic at high concentrations and may damage the tree near the infusion or injection ports (O. Batuman, *personal observations*; Reil 1979). In some instances, poor wound healing caused by injection ports allows wood-rotting organisms, or even ants, to invade, which can then produce lasting wounds.
5. Studies on antibiotic residues in fruit are limited: This may harm consumers and impact the marketability of the crops injected with antibiotics (Haynes et al. 2020). Despite these limitations, trunk injection tends to be more widely used in citrus. This is due to advances in the technology used for injections and the wide range of antibiotic formulations that are increasingly becoming available. Three new OTC formulations, ReMedium TI (TJ Biotech, LLC), Rectify (AgroSource, Tequesta, FL), and ArborBiotic (Invaio, Cambridge, MA), received special needs labels from the EPA for injection into citrus trees to combat HLB, with approvals granted in October 2022 and January 2023, respectively. Future research should focus on two main components of the injection system: injection tools to set up the injection port (drill versus non-drill based versus needle-based perforation) and associ-

TABLE 4
A summary of published studies for trunk injections of bacterial and phytoplasma/mycoplasma disease management in economically important crops

Crop	Disease	Pathogen	Concentration or rate	Use directions (injection device)	Antibiotic (trade name)	Reference(s)
Oxytetracycline and tetracyclines						
Apples	Fire blight	*Erwinia amylovora*	0.31 g + 2.52 ml of water	Quik-jet micro-injection system. Drilled 25.4 mm into the xylem tissue and 9.5 mm in diameter, with a cordless 1,500 rpm drill. Ports were sealed with plastic-silicone plugs (Arborplug No. 4, Arborjet).	Oxytetracycline hydrochloride 39.6% (ArborBiotic)	Aćimović et al. 2015
Peach	Peach X disease	*Mycoplasma* sp.	1 capsule/5-cm trunk diameter	A battery-powered drill was used to drill one to three 4.7-mm-diameter holes. Capsule tubes were inserted immediately after the holes were drilled and tapped with a mallet to make a tight fit at the insertion point. This tap also broke a seal where the tube was inserted into the capsule and allowed oxytetracycline solution to flow into the hole.	Polypropylene capsules (4 cm in diameter × 10 cm long, containing 6 ml of a 4% oxytetracycline	Cooley et al. 1992
Citrus (pomelo)	Huanglongbing/ citrus greening	'*Candidatus* Liberibacter asiaticus' (*C*Las)	2 g/liter (30 ml per tree)	AvoJect syringe injector (a catheter-tripped 60-ml syringe; Aongatete Coolstores Ltd., NZ). The tapered tip was fitted into a 19/4-inch (7.5-mm) diameter hole, approximately 3 cm deep, drilled into the tree.	Tetracycline, Bacbicure	Puttamuk et al. 2014
Citrus	Huanglongbing/ citrus greening	*C*Las	Varied based on antibiotic used	I.V. Micro Infusion (Arborjet) at <50 psi. Drilled holes on the trunk 30 cm below the first branch to a depth of 2 to 3 cm using a 7.14-mm drill bit; set No. 3 Arborplug into each hole for proper seal with Arborplug setter and a rubber hammer.AvoJect syringe injector (a catheter-tipped 60-ml syringe; Aongatete Coolstores Ltd., NZ). The tapered tip was firmly fitted into a 19/64-inch (7.5 mm) diameter hole, ~3 cm deep, drilled into the tree.	Oxytetracycline hydrochloride, (Arbor-OTC, Arborjet), tetracycline	Hu and Wang 2016; Li et al. 2019; Schwarz et al. 1974; Zhang et al. 2011, 2013
Citrus (sweet orange)	Huanglongbing/ citrus greening	*C*Las	6.25 to 12.5 mg/ml (200 ml/tree)	I.V. Micro Infusion (Arborjet) at <50 psi. Two injection ports per tree; 15 cm above the bud union, drilled at a depth of 20 to 30 mm with a 7.14-mm drill bit; drill site treated with Ridomil gold (Novartis).	Oxytetracycline hydrochloride, (Arbor-OTC, Arborjet)	Hu et al. 2018
Citrus (sweet oranges and grapefruit)	Huanglongbing/ citrus greening	*C*Las	2 g/liter (40 ml per tree)	Chemjet Tree Injectors (Logical Result, LLC) Chemjets (spring-loaded syringes) release liquid at 25 to 35 psi after activation. Drilled a 4.3-mm brad-point drill bit to a depth of 15 mm. Inserted Chemjet directly into the drilled hole at an angle of approximately 20 to 30 degrees and removed once all the compound was taken up by the tree. Used two Chemjets per tree for each injection; each Chemjet uses 20 ml of water or formulation dissolved in water.	Oxytetracycline hydrochloride (Arbor-OTC, Arborjet)	Archer and Albrecht 2023; Archer et al. 2023
Apricot	Apricot leaf roll disease	*Mycoplasma* sp.	1 g/tree (diluted in 1 liter of distilled water)	Effective for one season only.	Oxytetracycline hydrochloride	Rumbos 1986

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TABLE 4
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Crop	Disease	Pathogen	Concentration or rate	Use directions (injection device)	Antibiotic (trade name)	Reference(s)
Palm	Lethal bronzing	*Phytoplasma palmae*	5 ml at ~956 ppm of the solution injected into the base of the trunk every 3 months (quarterly)	Used a syringe. Used a 5/16-inch drill bit to create a 6- to 8-inch-deep hole. Effective as a preventive measure only.	Oxytetracycline hydrochloride (terramycin)	Harrison and Elliott 2008
Streptomycin						
Apples	Fire blight	*E. amylovora*	2 × 1.82 g/tree	Viper air/hydraulic micro-injection system (Arborjet) and Quik-jet micro-injection system (Arborjet). Drilled 25.4 mm into the xylem tissue and 9.53 mm in diameter with a cordless 1,500 rpm drill (DeWalt Industrial Tool Co.). Sealed ports with Arborplug No. 4 (Arborjet).	Streptomycin sulphate (agri-mycin; Nufarm, Ltd.)	Aćimović et al. 2015
Citrus (pomelo)	Huanglongbing/ citrus greening	*C*Las	A mixture of strepto-mycin (250 mg/liter), ampicillin (2.5 g/liter), and penicillin G (2 g/liter); 30 ml per tree	Injected in addition to penicillin and ampicillin. AvoJect syringe injector (a catheter-tripped 60-ml syringe; Aongatete Coolstores Ltd., NZ). The tapered tip was fitted into a 19/4-inch (7.5-mm) diameter hole, approximately 3 cm deep, drilled into the tree.	Streptomycin	Puttamuk et al. 2014
Citrus	Huanglongbing/ citrus greening	*C*Las	1.20 g/liter per tree	Tree I.V. (Arborjet). Drilled a hole on the trunk 20 cm below the first branch to a depth of 2 to 3 cm using a 7.1-mm drill bit. A No. 3 Arborplug was set into the hole to seal with an Arborplug setter and a rubber mallet.	Streptomycin (FireWall 50 WP, AgroSource)	Li et al. 2021a
Citrus (sweet orange)	Huanglongbing/ citrus greening	*C*Las	6.25 to 12.5 mg/ml (200 ml/tree)	I.V. Micro Infusion (Arborjet) at <50 psi. Two injection ports per tree; 15 cm above the bud union, drilled at a depth of 20 to 30 mm with a 7.14-mm drill bit. Drill site treated with Ridomil gold (Novartis).	Streptomycin sulfate salt (Sigma-Aldrich)	Hu et al. 2018
Citrus (sweet orange)	Huanglongbing/ citrus greening	*C*Las	0.5, 1.0, and 2.0 g/tree; 300 ml/tree	Tree I.V. (Arborjet) at the recommended pressure (~345 kPa); trunk was drilled 20 cm below the first branch to a depth of 2 to 3 cm using a 7.1-mm drill bit. A No. 3 Arborplug was set into the hole for a proper seal.	Streptomycin sulfate, laboratory grade (Thermo Fisher Scientific)	Li et al. 2021a
Kasugamycin						
Apples	Fire blight	*E. amylovora*	2 × 7.6 ml (injected with 520 ml of water per tree)	Used Tree I.V. injection system.Drilled 25.4 mm into the xylem tissue and 9.5 mm in diameter with a cordless 1,500 rpm drill. Ports were sealed with plastic-silicone plugs (Arborplug No. 4, Arborjet).	Kasugamycin hydrochloride 2.3% (Kasumin 2 liters)	Aćimović et al. 2015
Citrus	Huanglongbing/ citrus greening	*C*Las	1 g per tree	Used in combination with oxytetracycline.AvoJect syringe injector (a catheter-tipped 60-ml syringe; Aongatete Coolstores Ltd., NZ). The tapered tip was firmly fitted into a 19/64-inch (7.5 mm) diameter hole, ~3 cm deep, drilled into the tree.	Kasugamycin	Zhang et al. 2013

ated injection devices to deliver the antibiotics (syringe, open tank, pressurized capsule, etc.).

Overall, the use of trunk injection as a plant disease management tool is growing and is likely to be widely implemented for certain tree crops. Automated delivery systems that help growers inject therapeutics into tree crops of large production orchards are needed. Thus, we are currently in the process of developing an automated delivery system that will help growers deliver various therapeutics, including antibiotics, into mature commercial citrus trees affected with HLB in the near future (Ojo et al. 2024b).

Antibiotics detection and residue analysis in plants

Antibiotic residue buildup on citrus fruit and juice treated by trunk injection is a critical concern for growers, the industry, and the public. Consumers of these treated crops are concerned about the potential health effects of these residues. To address these concerns, several detection methods have been developed to help identify and quantify antibiotic residues in plants, including liquid chromatography-mass spectrometry, high-performance liquid chromatography, and immunoassays (such as the enzyme-linked immunosorbent assay) (Hijaz et al. 2021a, b, c).

Although there have been a few studies on the accumulation and distribution of antibiotics when injected into fruit trees, such studies are limited (Hijaz et al. 2021b; Hu and Wang 2016; Li et al. 2019, 2021a). The maximum residue limit of OTC in apple, peach, and pear fruit is 0.35 ppm (0.35 μg/g), and there are no reports of OTC residues approaching this limit in these crops. However, only 0.01 ppm (0.01 μg/g) can be allowed for citrus fruit, although it was temporarily increased to 0.4 ppm under emergency exemption section 18, which expired in 2020 (https://www.ecfr.gov/). Li et al. (2019) found that the average amount of OTC residues in citrus fruit at harvest was 0.018 and 0.038 μg/g for trees 9 months after injecting them with either 0.25 or 0.50 g/tree, respectively. These residue levels are above the U.S. maximum residue limit of 0.01 μg/g as set by the EPA. Sruamsiri et al. (2013) found that after 60 days of injection of tetracycline at a dosage of 12,500 μg/ml in 40 ml (0.5 g/tree), citrus fruit contained 0.12 μg/g of tetracycline content, which decreased significantly after 90 days.

We recently investigated the buildup of OTC residues in three varieties of citrus fruit collected at various intervals and found that antibiotic levels varied among tissue type, variety, and season (Archer et al. 2023). We found the residue levels ranging from less than 0.1 to 0.6 μg/g across all three citrus varieties. Li et al. (2021a) showed that a single trunk injection of streptomycin into 3-year-old Valencia citrus trees at 2.0 g/tree resulted in the accumulation and persistence of sufficient levels of streptomycin, which was enough to provide season-long suppression of *C*Las populations, with a residue level below the EPA's maximum residue limit (2.0 μg/g) in harvested fruit. Ark and Alcorn (1956) found that streptomycin could be recovered from pear leaves even up to a year after the antibiotic had been delivered through an artificial hole in the tree's trunk. Our field trial results indicated that OTC residues in fruits decrease dramatically within 30 to 60 days after injection.

In conclusion, it is important to consider the effect of injection method, dosage, timing, and tree size on antibiotic residue levels over time to ensure acceptable residues at harvest for each crop type. Our preliminary field results indicate that the citrus fruits following the spring injection were larger than citrus fruits after the fall injection, suggesting that the timing of injections may affect fruit size and quality. Likewise, the degradation rate of antibiotics in fruit remains unknown for most crops, which will need investigation in the future. Developing analytical instruments with improved sensitivity and selectivity is critical for detecting low concentrations of antibiotics in complex environmental matrices. We are currently developing effective antibiotic detection methods and studying residue and degradation periods of several antibiotics in citrus groves.

Environmental Impacts of Antibiotics

The environmental impacts of antibiotics used in plant agriculture and the risk factors related to their application continue to be critical subjects. Although the amount and variety of antibiotics used on plants are low compared with other agricultural sectors, there are rising concerns about ARG accumulation and off-target effects on the environment (Chen et al. 2019; McManus et al. 2002; Sundin and Wang 2018). According to models from the U.S. EPA, human exposure from medical use of antibiotics is several thousand-fold more than from antibiotics used for disease management in plant production (U.S. EPA 2006, 2008). Researchers have also demonstrated that streptomycin use did not increase the abundance of mobile ARGs (Duffy et al. 2014); nevertheless, caution for antibiotic use in plant agriculture and potential environmental residues should still be a priority. This section will address the documented environmental impacts of antibiotics used in plant agriculture.

ARG accumulation

Negative effects and potential threats to human health cannot be attributed to selection pressure favoring ARB pathogens due to the antibiotic applications on plants (McManus et al. 2002). Therefore, one of the greatest concerns of antibiotic use in plant production is the risk of incidence, accumulation, and deposition of ARGs in the food chain and the soil environment (Chen et al. 2019), but this concern was not observed in apple orchards treated with streptomycin (Duffy et al. 2014). Although not yet seen in plant agriculture, it is important to remember that a high incidence of ARGs poses a greater risk of a resistance gene transfer to medically important bacteria (Allen et al. 2010; Cantas et al. 2013; Forsberg et al. 2012). The plant microbiome potentially containing ARB plays a crucial role in connecting human and natural microbiomes by creating pathways for human exposure to environmental antibiotic resistance (Abriouel et al. 2008; Marti et al. 2013). Direct contact, food chain, international trade, and globalization exacerbate the distribution of ARGs present in plant-associated microorganisms (Chen et al. 2019).

Wastewater-treatment plants, operations producing concentrated animal feed, and animal manure are some of the important reservoirs of ARGs (Baquero et al. 2008; Rizzo et al. 2013; Su et al. 2017; Zhu et al. 2013). Antibiotics used in veterinary medicine or as growth promoters can remain in manure even after being excreted by the animals and subsequently used as agricultural fertilizer. Studies have shown that tetracyclines are strongly absorbed and persistent in manure and soil (Blackwell et al. 2005; Loke et al. 2002). The potential spread of ARGs in the water and the soil environment from agricultural organic fertilization (such as manure and biosolids) has been previously investigated using metagenomic studies. These studies provide evidence that animal manure and sewage sludge contain ARGs and that the long-term application of the manure and sludge has increased the abundance of ARGs in the soil environment and phyllosphere (Chen et al. 2016; Fahrenfeld et al. 2014; Udikovic-Kolic et al. 2014). In the case of organically produced lettuce, the abundance of ARGs was found to be approximately eight times higher than in conventional production (Zhu et al. 2017). On the other hand, the foliar application of OTC and gentamicin on coriander plants had no significant effect on the abundance of resistant bacteria and the ARGs (Rodríguez-Sánchez et al. 2008). Large functional overlap between the phyllosphere and rhizosphere bacteria suggests that bacteria move either from soil to the leaves or vice versa (Bai et al. 2015; Ruiz-Pérez et al. 2016). Bacterial movement between soil and plants may contribute to the increased abundance of ARGs in the soil environment and phyllosphere (Zhu et al. 2017). Another contributing factor to ARG environmental accumulation can be when such soil bacteria are transmitted by aerosols during agricultural activities, which then serve as important reservoirs of ARGs and their transfer (Bulgarelli et al. 2013; Vorholt 2012).

The recent evolution of global antibiotic resistance is mainly associated with gene transfer within bacterial communities (Sundin and Bender 1996). The prevalence of transmissible ARGs was previously observed in bacterial communities in orchards, phylloplanes, and soil environments (Duffy et al. 2011; Heuer et al. 2002; Popowska et al. 2012; Schnabel and Jones 1999). For example, *strA-strB* are widely distributed genes that encode for enzymes that modify streptomycin by phosphorylation and reduce its antibacterial activity (Petrova et al. 2008; Tancos et al. 2016; van Overbeek et al. 2002). The prevalence and wide distribution of these resistance genes in different environments suggest that gene transfer between human, plant, and other host-associated bacteria is possible (Sundin and Bender 1996). Previously, the transfer of the tetracycline-resistance (Tc^R) plasmid to human- and plant-origin enteric bacteria was demonstrated at different frequencies in laboratory studies (Chatterjee and Starr 1972). Although broad-host-range gene transfer between bacterial communities has been demonstrated under laboratory conditions, the severity, span, and biological significance of the HGT events in nature remains unknown.

Off-target effects

The abundance and diversity of microorganisms are essential determinants for better soil quality and plant health (Nannipieri et al. 2003; Nielsen et al. 2002). Residues from antibiotics used in agricultural practices may potentially alter the nontarget microbial community profile, including beneficial bacteria present in the phytobiome, soil, and water. Previously, it was shown that the short-term (2 years) aerial application of streptomycin on nontarget bacterial communities was found to have minimal—if any—consequences for apple orchard soil bacterial communities (Duffy et al. 2011). Another study showed that the streptomycin application had no detectable effect on the abundance of ARGs and bacterial communities associated with apple leaves, twigs, or flowers (Shade et al. 2013). The limited studies conclude that the use of antibiotics in plant disease management had minimal effect on altering the bacterial communities in the phytobiome, soil, and water.

Furthermore, several reports demonstrate the effect of experimental trunk injections of antibiotics on citrus microbial communities, specifically causing decreases in bacterial abundance and composition (Ascunce et al. 2019; Shin et al. 2016; Zhang et al. 2013). Bacterial diversity was also affected in some studies from antibiotic trunk injections, though with the use of unregistered antibiotics for citrus and with additional influence from the environment (time of year), host, and quantification methods (Ascunce et al. 2019; Zhang et al. 2013). Little is known, however, about soil microbiome effects regarding this application method, but research will likely emerge as Florida citrus growers continue to prioritize this control against HLB-affected citrus.

Economics of Antibiotics

Antibiotics are predominantly used in tree fruit agriculture for controlling plant bacterial diseases. For example, antibiotics have been mostly used for controlling the fire blight disease in apples and pears, with close to 20% of the total apple production using OTC and streptomycin (Granatstein et al. 2013). Because the use of antibiotics is driven by the necessity to prevent and control diseases, their use is restricted to certain fruit in specific geographical locations. Given their limited use, information on the economics of using antibiotics is scant. Thus, growers who plan to use antibiotics in their orchards face uncertainty regarding the costs and benefits associated with their adoption, as well as the market perception of fruit produced with antibiotics. In this section, we summarize the most relevant research findings on the economics of antibiotic use in U.S. plant agriculture and tree fruit production.

Costs of antibiotic use

Almost all antibiotics are used prophylactically (except for OTC trunk injections against HLB-affected trees), and they do not provide any cure when applied to infected trees (Smits et al. 2014; Stockwell and Duffy 2012). Efficient application of antibiotics requires correct prediction of factors that are conducive to the growth of disease-causing bacteria and selecting trees that are more vulnerable to infection, such as pome fruit trees in full bloom (Billing 2007). Therefore, a grower would choose to use antibiotics depending on the prevalence and the severity of a disease, weather, and other exogenous factors impacting disease spread. Harvest timing, such as preharvest intervals, and market conditions will also have to be considered. Fruit trees take, on average, 3 to 5 years to become productive; a single event of a disease such as fire blight could destroy substantial investments that a grower made to develop an orchard. When a grower decides to grow organic fruit, which by law prevents the grower from using antibiotics (with organic apples and pears as exemptions until 2014), in the event of a disease outbreak, they will have to choose between losing their trees or losing their organic certification for at least 3 years if they decide to use antibiotics for new trees.

A key challenge in the use of antibiotics is the lack of enterprise budgets and published cost-benefit analyses of applying antibiotics in overall fruit production. However, several enterprise budgets on apple that include the costs of using antibiotics are available. Kasumin 2L, containing the antibiotic kasugamycin, is one of the primary bactericides used in the production of pome fruit and walnuts. Researchers at the Washington State University Extension report that Kasumin 2L is applied twice per year and costs a total of $127.36 per year per 0.4 ha (1 acre) of apple orchard where apples are grown using the vertical trellis system (Washington State University Extension, *unpublished data*). Budgets for conventional apple production systems consider the costs of applying antibiotics, and, when compared with an organic production system that does not use antibiotics, the variable costs of producing conventional apples are lower than those of organic apples (Gallardo and Galinato 2020). Although antibiotics are sprayed in apple and pear production, using trunk injections for delivering antibiotics was found to be more effective in controlling fire blight disease (Aćimović et al. 2015). Trunk injections are also used in avocado production to deliver fungicides to control laurel wilt disease (Ploetz et al. 2011). Although injecting Tilt and phosphate into avocado trees increases the per-hectare cost of production by $600, the improved yields increase the net returns by over $1,300 per 0.4 ha (or an acre).

In Florida citrus production, several researchers found that injecting OTC is effective in suppressing the *C*las bacteria that cause HLB (Archer et al. 2021, 2023; Hu and Wang 2016; Li et al. 2019). As previously mentioned, in 2022 and 2023, the EPA and Florida Department of Agriculture and Consumer Services approved several OTC antibiotic products as a special local need for the citrus industry in Florida. Few studies published costs for technology or practice adoption in citrus. For example, Chakravarty and Wade (2023) estimated the costs of adopting cover crops in citrus production. However, currently, there are no studies that estimate the costs of using trunk injections for delivering antibiotics into citrus trees. Preliminary data from the University of Florida indicate that, on average, OTC trunk injections in citrus cost $1.08 per tree. This ranges from $100 to $200 per 0.4 ha (1 acre), depending on the tree density and the size of the operation. Labor costs comprise around 45% of the total OTC injection costs, whereas chemical and device costs are around 25% each. Machinery and fuel costs are around 5% of the total costs. OTC trunk injection is a new production practice in citrus, and management costs will likely decrease as producers become more efficient.

During the development of this review, another preliminary study on OTC injection-associated costs in Florida citrus was reported (Singerman 2023). In this study, depending on multiple factors, such as tree trunk diameter, amount of OTC injected, and tree density in groves, the total cost of OTC injection per 0.4 ha (1 acre) was estimated to be between $202 and $255. The cost of the compound used in this study was $106 per 0.4 kg based on the average of the less expensive products available on the market. Furthermore, the same study found that if the grower's yield were equal to the 2022/23 Florida statewide (average) yield for Valencia oranges (51 boxes/acre; 1 box contains 40 kg of fruits, and an acre is 0.4 ha), the expected additional yield would only allow the grower to offset the cost of the treatment in the first year but may result in a profit in the second year. If the grower's yield exceeds the state average, the treatment may be profitable in both the first and second years.

Marketability of the treated produce

Among the various attributes of food, it was found that consumers value safety, nutrition, taste, and price more than other attributes, such as fairness, tradition, and origin (Lusk and Briggeman 2009). The marketability of fruit from antibiotics-treated orchards will depend on consumer perception of the treated fruit trees. Although current laws do not require producers to disclose antibiotic use in conventional fruit production to consumers, information on permitted residual levels of antibiotics in fruit and their health effects on humans is available. Studies indicate that fruit with maximum permissible levels of antibiotic residues will have no negative effect on human health. For example, to reach the level of the acceptable daily intake of tetracycline residues, a person weighing 100 kg would have to consume 7 kg of apples with the permitted tolerance level of 0.35 mg/kg fruit in a single day (Stockwell et al. 2013).

Antibiotics are used more widely in animal production systems than in fruit production (Stockwell and Duffy 2012). Therefore, much of what we know about consumers' perceptions of antibiotics in foods comes from the literature related to animal production. Consumer awareness of antibiotic use in the meat and milk industries is significantly higher than that in fruit production, and studies on consumer perceptions of antibiotics in food have been restricted to these production systems. For example, a seminal study found that consumers are willing to pay significant premiums for pork produced without antibiotics and would value a ban on antibiotic use in meat production (Lusk et al. 2006). Given that meat and milk sold in the United States are free of antibiotic residues, by federal law, such studies imply that consumers are concerned about the use of antibiotics in the production process itself, even if the final product does not contain antibiotic residues. Research that studied consumers' willingness to pay for organic, GMO-free, and local produce showed that although consumers are willing to pay substantially more for such products than those without such labels, their willingness to pay depends on multiple sociodemographic characteristics, such as income, age, occupation, and geographic location, among others (Batte et al. 2007; Carpio and Isengildina-Massa 2009; Loureiro and Hine 2002). Furthermore, consumers are driven by personal values, such as security in the form of health safety, taste, benevolence, and concern for people and the environment, when choosing organic food for consumption (Aertsens et al. 2009).

Given the lack of information on antibiotic use in fruit production and the lack of labeling, consumers who value safety and nutrition more than other attributes of food may view the use of antibiotics in fruit production as negative and may be willing to pay a premium for fruit produced without antibiotics. Additionally, concerns over the spread of antimicrobial-resistant bacteria in the environment through the use of antibiotics in agriculture could impact consumer perceptions, even though the direct impacts of antibiotic residues in food on human health are negligible. Thus, recent media reports, such as Dall (2019) and Jacobs (2019), raise issues on the environmental health concerns of using antibiotics in fruit production and how these concerns could shape consumer preferences.

To our knowledge, no laws require informing consumers about antibiotic use in fruit production. Because fruit labels do not indicate whether the fruit is grown in orchards treated with antibiotics (other than organic fruit, which in turn do not use antibiotics), consumers may not encounter produce that is marked as antibiotic-treated. Even though antibiotic use with permitted residue levels is not a cause of concern for human health, studying consumers' perceptions and willingness to pay for fruit without antibiotic treatment will depend on the information provided to them, their inherent disposition toward antibiotic use, and pricing. To effectively market fruit from orchards treated with antibiotics, sellers will have to address consumer concerns about both the direct and indirect effects of antibiotics on human health and the steps being taken to minimize the impacts of antibiotics.

Concluding Remarks

Antibiotics in plant agriculture will remain a valuable tool in our fight against phytopathogenic bacteria. Although studies have shown little environmental impact from antibiotics used in crop production, it would still be in our best interest to continue to study ecological residues, monitor resistance development in bacterial target populations, and integrate non-antibiotic alternatives into disease control. Such steps can help with ensuring antimicrobial efficacy for the future. Policies surrounding antibiotics in plant agriculture can also benefit from a more globalized set of regulations, as well as increase consumer trust and awareness regarding their use. Finally, the current development of efficient delivery systems (specifically trunk injection) for antibiotics will enhance the control of certain diseases by antibiotics, especially against the devastating HLB disease in Florida citrus.

Acknowledgments

We thank research faculty collaborators and their program members across multiple campuses of UF-IFAS for their contributions to the study and numerous Florida citrus growers and industry members for their ongoing support and collaboration with all studies conducted with their help and donations. We also thank *Phytopathology* Editorial Board members, notably Nian Wang, for the invitation and opportunity to highlight our studies. We also acknowledge and appreciate anonymous reviewers' time, critical comments, and valuable suggestions extended to us to improve our review article.

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