PLANTIBIO project for **PL**ant (pathogenic bacteria) **ANTIBIO**tic (resistance)

Reduce risk assessment uncertainties: data collection on antibiotics for control of plant pathogenic bacteria

Abstract *:* There is a lack of data on antimicrobial use despite evidence on a key role of environnement in the emergence of resistance to antibiotics. The European Food Safety Authority has launched a project for a global data collection on the use of antibiotics and the emergence of antimicrobial resistance in plant pathogenic, with a particular focus on plant pathogenic bacteria causing systemic plant diseases. Emerging and re-emerging systemic plant pathogenic bacteria are nowadays a growing concern because of the difficulties to control them in the agriculture and in the environment and because of their capacity to rapidly spread into new areas by means of global trade of infected plants. Countries are invited to contribute by providing information on antibiotic used as plant protection products or *participate to the workshop organized* as a satellite event of the EFSA ONE conference in Brussels on June 21st, 2022 and entitled '*How does antibiotic resistance in plant pathogenic bacteria impact 'One Health'?*

Keywords: Antibiotic, Antibiotic resistome, Antimicrobial resistance, bactericide, control measures, Plant pathogenic bacteria.

Bacterial diseases are on the rise, move with plant for planting material, but remain difficult to control – a major challenge for risk management in plant health

Plant pathogenic bacteria (PPB) cause devastating losses to crops worldwide, estimated over one billion dollars every year (Mansfield et al., 2012; Kannan et al., 2015). Some of these plant pathogenic bacteria constitute a major concern as plant quarantine agents, such as *Xylella fastidiosa*, causal agent of the Pierce's disease of grapevine, the Huanglongbing or citrus greening disease caused by *Candidatus* Liberibacter asiaticus or the Potato Zebra chip caused by *Candidatus* Liberibacter solanacearum, or the numerous *Candidatus* Phytoplasma evidenced so far. All these bacteria are systemic in their host with an urgent need of effective control measure. Furthermore, the analysis of the global trends in emerging infectious diseases reveals an increasing number of infections linked to plant pathogenic bacteria (Savary et al., 2019).

Antibiotics are used against some bacterial plant pathogens. Oxytetracycline is permitted on crops in the USA, Mexico, and Central America. Oxolinic acid (a quinolone antibiotic) is used in Japan and Israel on rice and pome fruits, respectively. Gentamicin is used in Mexico and Central America and Kasugamycin is registered in Canada (Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges, 2018). Streptomycin is registered for the control of fire blight of pear and apple, caused by *Erwinia amylovora* in North America, New Zealand and Israel (Stockwell and Duffy, 2012). Antibiotics are currently not authorised in Europe for plant protection except tightly regulated emergency uses against fire blight (*Erwinia amylovora*) in some countries.

Generally, only a limited number of antibiotics are authorized for plant protection, from a limited number of classes of antibiotics, such as tetracyclines, aminoglycosides and quinolones. A recent study from an international database of agronomic advice to farmers shows, however, that antibiotics may be recommended far more frequently and on a much greater variety of crops than previously thought (Taylor et al., 2020).

Antibiotic resistance is recognized as a major crisis in relation to human health (Ventola, 2015) and strategies are developed in order not to lose antibiotics as an efficient treatment of human and animal diseases (WHO, 2001; Smith and Coast, 2002). The European Commission has developed an action plan against antimicrobial resistance in the context of a one health initiative with the aim to make the EU a best practice region, boosting research, development and innovation and shaping the global agenda (https://ec.europa.eu/health/amr/antimicrobial-resistance_en).

The use of antibiotics in plant protection is one of the potential causes of an increase in antimicrobial resistance genes in the environment. An increased use of antimicrobial substances as pesticides could undermine the efficiency of antibiotic therapy in humans (Curutiu et al., 2017). Streptomycin resistant strains of *Erwinia amylovora* were found in pear orchards where streptomycin was applied (Loper et al., 1991). In addition to *Erwinia amylovora*, streptomycin resistance genes were also found in *Pseudomonas syringae* and *Xanthomonas campestris* (Sundin and Wang, 2018). Other studies did not find a significant increase of resistance genes after antibiotic treatments in orchards (Duffy et al., 2014)

The efficiency and potential risks from the use of antibiotics in plant protection is under scientific debate. A recent example are the emergency applications of Tetracyclines and Streptomycin against Citrus greening in the USA (McKenna 2019). Some studies conclude that antibiotics are essential for treatment of some plant diseases and that antibiotics decline rapidly on the treated plants, without changing the microbial communities and that there are no adverse effects on human health or persistent impacts on the environment (Stockwell and Duffy, 2012; Stockwell, 2014). While other researchers question the efficacy of antibiotic treatments (Vidaver, 2002) and observed long persistence of antibiotics after trunk treatments in citrus trees (Hu and Wang, 2016). A joint investigation by the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE) and the World Health Organization (WHO) on the antibiotic use, stated that the use of antibiotic currently used in crop cultivation is considered as very low in comparison to antibiotic use in both veterinary and medical fields (FAO and WHO, 2019). Similarly, Sundin and Wang (2018) reported limited use of antibiotic in crop protection, targeted to a limited number of bacterial diseases and high value crops. But a recent study by Taylor and Reeder (2020) suggested that the antibiotic use for crop protection is much more widespread than previously thought. These divergences are maybe also the result of major differences in the way antibiotics are registered for use the plant protection area. While the terms ‘antibiotic’ or ‘antimicrobials’ are commonly used in animal and human health, the general terms pesticide, plant protection products (PPP) or more specifically bactericide are common in the plant protection field. Also, the term "bactericide" is very often grouped with the term "fungicide", since sometimes a given molecule shows effect on both bacteria and fungi. The same confusion also exists for the term "biocide" with slightly different definitions in Europe vs. USA (US Environmental Protection Agency - EPA). This is also highlighted by the fact that in many countries, there is no legislation in place with regards to the use of antibiotics as plant protection product (Haynes et al., 2020). Furthermore, the distribution of antibiotics, even unauthorized, via companies operating online or providing alternatives marketing options like recently evidenced in Thailand (Chanvatik et al., 2019) remains an issue.

Alternatives to antibiotic treatments in plant protection are being researched and are under evaluation (e.g. see: Johnson and Temple, 2013; EFSA PLH Panel et al., 2019) and some of the alternative treatments e.g. copper may lead to cross resistance to antibiotics (Scheck et al., 1996). Strategies such as integrated pest and disease management (IPM), planting

resistant cultivars, pathogen exclusion, crop rotation and soil improvement are suggested to reduce or eliminate the need to use antimicrobials in plant protection (Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges, 2018).

Given the new global emergency of highly destructive bacterial plant pests (e.g. Xylella, HLB), the Scientific Panel on Plant Health of the European Food Safety Authority (EFSA) has considered conducting a comprehensive analysis of the efficacy and the risk of development of antimicrobial resistance in plant pathogens one of the future challenges and priorities for plant health risk assessment.

MAIN OBJECTIVE AND SCOPE OF THE PROJECT

For the above reasons, EFSA has launched in 2019 a Call for proposals for a global data collection on the use of antibiotics and the emergence of antimicrobial resistance in plant pathogenic, with a particular focus on plant pathogenic bacteria causing systemic plant diseases.

Emerging and re-emerging systemic plant pathogenic bacteria are nowadays a growing concern because of the difficulties to control them in the agriculture and in the environment and because of their capacity to rapidly spread into new areas by means of global trade of infected plants. Recent examples were the introduction of *Xylella fastidiosa* into Mediterranean and Middle East orchards and of the citrus greening bacterium *Candidatus* Liberibacter asiaticus into most of the citrus growing areas. By collection and review of information and data, uncertainties on the control of systemic plant pathogenic bacterial diseases can be reduced, thus increasing preparedness to address new and emerging plant health risks and also supporting prioritization of future research. In particular, this PLANTIBIO project aims to collect data and information, in the context of plant pathogenic bacteria, on the effectiveness of antibiotic treatments, on the development of resistance to antibiotics and also on the availability and effectiveness of alternative treatments for control of plant pathogenic bacteria. This will also contribute to a better understanding of antibiotic resistance in plant pathogenic bacteria in the context of the one health and antimicrobial resistance initiative.

*The **PLANTIBIO** project, supported by EFSA and conducted by the Université catholique de Louvain (**UCLouvain**) in Belgium, aims at understanding how and how much antibiotics are used to control PPB, resistance to antibiotics registered, applied or developed for the control of plant pathogenic bacteria, as well as collecting data and information on alternative control measures for systemic plant pathogenic bacteria*

Understanding how and how much antibiotics are used to control plant pathogenic bacteria, resistance to antibiotics registered, applied or developed for the control of plant pathogenic bacteria, as well as collecting data and information on alternative control measures for systemic plant pathogenic bacteria will help assessing the sustainability for plant pathogenic bacteria control and the risk of antimicrobial resistance in plant pathogenic bacteria, in the context of One Health approaches, as well as antimicrobial resistance initiatives. Control of plant pathogenic bacteria has always been a challenge in plant protection. Usually orientated towards prophylactic measures combined to plant resistance, the number of direct or curative control strategies is limited. The need for alternative control measures and novel tactics is even stronger, considering not only the increasing resistance to existing bactericides, but also the new and emerging bacterial disease problems. The PLANTIBIO project aims at unravelling the uncertainties affecting the assessment of risk reduction options for systemic plant pathogenic bacteria, as well as at increasing awareness and preparedness for new and emerging diseases.

SPECIFIC OBJECTIVES OF THE PLANTIBIO PROJECT

This project addresses three specific objectives:
• Specific Objective 1: collection and review of data and information on the use of antibiotics for the control of plant pathogenic bacteria
• Specific Objective 2: collection and review of data and information on resistance to antibiotics in plant pathogenic bacteria
• Specific Objective 3: collection and review of data and information on alternative and innovative treatments for the control of systemic plant pathogenic bacteria

Specific Objective 1: collection and review of data and information on the use of antibiotics for the control of plant pathogenic bacteria

Objective 1 is to search, collect and review worldwide information and data from scientific literature, technical and grey (i.e. not peer-reviewed) literature, databases, patents, websites and other available sources on the antibiotics registered, applied or developed for the control (including also prophylactic use) of plant pathogenic bacteria. This objective is not restricted to bacteria causing systemic plant diseases but covers applications of antibiotics for control of any plant pathogenic bacteria. In particular, this objective includes the following:

• Collection and review of data and information on the worldwide registration of antibiotics in plant protection for the control (including also prophylactic use) of plant pathogenic bacteria.

• Collection and review of data and information on the worldwide application/use of antibiotics in plant protection for the control (including also prophylactic use) of plant pathogenic bacteria.

• Collection and review of data and information on the effectiveness and, when applicable, side effects, of the various antibiotic treatments (including prophylactic use) and of their application methods against plant pathogenic bacteria.

• Collection and review of data and information on short and long-term changes in microbial communities in the agricultural environment due to antibiotic use in plant protection (including data available on potential impacts on microbial communities, alteration of competition among microbes and changes in supporting and regulating ecosystem services).

Specific Objective 2: collection and review of data and information on resistance to antibiotics in plant pathogenic bacteria

Objective 2 is to search, collect and review worldwide information and data from scientific literature, technical and grey (i.e. not peer-reviewed) literature, databases (including gene banks), websites and other available sources on the resistance to antibiotics registered, applied or developed for the control of plant pathogenic bacteria. This objective is not restricted to bacteria causing systemic plant diseases and covers resistance to antibiotics of any plant pathogenic bacteria.

• Collection and review of data and information on the occurrence and frequency of antibiotics resistance among plant pathogenic bacteria, by search of scientific literature, technical and grey literature, databases, websites and other available sources.

• Collection and review of data and information on the occurrence and frequency of antibiotics resistance, by search in gene banks in genomes of plant pathogenic bacteria

• Collection and review of data and information on resistance development in plant pathogenic bacteria due to the use of antibiotics in plant protection

• Collection and review of data, information and models on the possible transfer of antibiotic resistance from/to plant pathogenic bacteria, in particular: from plant pathogenic bacteria in the agriculture environment towards bacterial communities in animals and humans; towards plant pathogenic bacteria from other sources (e.g. animals, humans or environment).

Specific Objective 3: collection and review of data and information on alternative and innovative treatments for the control of systemic plant pathogenic bacteria

Objective 3 is to search, collect and review worldwide information and data from scientific literature, technical and grey (i.e. not peer-reviewed) literature, databases, patents, websites and other available sources) on the effectiveness and, when applicable, side effects of innovative methods, alternative to antibiotics treatments, for the control (including also prophylactic use) of systemic plant pathogenic bacteria. In particular, this objective includes the following:

• Collection and review of data and information on the effectiveness and, when applicable, side effects of alternative and innovative treatments for the control (including also prophylactic use) of systemic bacterial plant diseases, from scientific peer reviewed literature

• Collection and review of data and information on the effectiveness and, when applicable, side effects of alternative and innovative treatments for the control (including also prophylactic use) of systemic bacterial plant diseases, from technical and grey (not peer-reviewed) literature, databases, websites and other available sources

• Collection and review of data and information on the effectiveness and, when applicable, side effects of alternative and innovative treatments for the control (including also prophylactic use) of systemic bacterial plant diseases, from registration and labels.

• Collection and review of data and information on the effectiveness and, when applicable, side effects of alternative and innovative treatments for the control (including also prophylactic use) of systemic bacterial plant diseases, from patents.

• Summary and review of search results on the effectiveness of alternative and innovative treatments for control of systemic bacterial plant diseases from the different sources above, including the identification of best search strategies and discussion of advantages and limitations for each type of sources.

How to contribute to the PLANTIBIO project ?

Provide information to PLANTIBIO project:
Countries are invited to contribute by providing information on antibiotic substances used as plant protection products (commercial names for antibiotic, formulation, bacterial disease targeted, host plants, mode of application, companies commercializing the product, amount of antibiotic commercialized per year). The easiest way to participate is to provide the name and contact details at the email plantibio@uclouvain.be or to send the requested information by using the same email. All contributors will be acknowledged.

Participate to the next PLANTIBIO workshop on 21 June 2022:
A workshop is organized as a satellite event of the EFSA ONE conference in Brussels on June 21st, 2022. ***How does antibiotic resistance in plant pathogenic bacteria impact 'One Health'?***

The objective of the workshop is to encourage the exchange and collection of data on:

i) the use of antibiotics for controlling plant pathogenic bacteria;
ii) the antibiotic resistance in plant pathogenic bacteria; and
iii) alternative measures for controlling plant pathogenic bacteria, with an emphasis on data gaps and key questions for improving risk assessment.

The workshop also aims to establish the basis for a network on the topic, connecting with established networks in the areas of animal and human health.

As part of the workshop, global inventories of antibiotics used as plant protection products and information on antimicrobial resistance associated with the use of antibiotics in plant protection collected by the PLANTIBIO project will be presented.

If interested, please consult the conference website at https://www.one2022.eu/side-events and do not hesitate to register. The workshop might be attended physically or remotely, via webstreaming.

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