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PERSPECTIVES

The Epidemiology of *Xylella fastidiosa*; A Perspective on Current Knowledge and Framework to Investigate Plant Host–Vector–Pathogen Interactions

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ABSTRACT

Insect-transmitted plant diseases caused by viruses, phytoplasmas, and bacteria share many features in common regardless of the causal agent. This perspective aims to show how a model framework, developed originally for plant virus diseases, can be modified for the case of diseases incited by *Xylella fastidiosa*. In particular, the model framework enables the specification of a simple but quite general invasion criterion defined in terms of key plant, pathogen, and vector parameters and, importantly, their interactions, which determine whether or not an incursion or isolated outbreak of a pathogen will lead to establishment, persistence, and subsequent epidemic development. Hence, this approach is applicable to the wide range of *X. fastidiosa*-incited diseases that have recently emerged in southern Europe, each with differing host plant, pathogen subspecies, and vector identities. Of particular importance are parameters relating to vector abundance and activity, transmission characteristics, and behavior in relation to preferences for host infection status. Some gaps in knowledge with regard to the developing situation in Europe are noted.

In recent years, there has been a marked increase in interest and attention given to newly emerging vectored diseases of plants, animals, and humans (Jones et al. 2008), including those caused by viruses. This is also of interest for important insect-transmitted bacterial diseases of plants. For example, in a general review of insect-transmitted bacterial diseases of plants, including *Xylella fastidiosa*, *Spiroplasma* spp., *Liberibacter* spp., and phytoplasmas, Perilla-Henao and Casteel (2016) pointed out that less work has been done compared with vectored virus diseases of plants. Similarly, in a general review of phloem-limited pathogens, Bendix and Lewis (2018) pointed out the commonalities between bacteria and viruses in their virulence strategies and posited that such commonality may form the basis for disease management strategies that are widely applicable. Interactions among plants, vectors, and bacteria are often poorly understood (Tamborindeguy et al. 2017) and constrain the ability to control the newly emerging diseases that result. The review by Tamborindeguy et al. (2017) focuses on the influence of bacteria on multitrophic interactions among plants, psyllids, and pathogens and stress that, as more organisms are studied, subtleties of the molecular interactions as well as of the effect of the bacteria on the psyllid host are being uncovered. Furthermore, the review underlines gaps and lags in knowledge that may arise because the disease is newly emerging.

As with plant viruses, transmission of plant-pathogenic bacteria by insects goes beyond a purely physical association between vector and bacterium and involves aspects of host modulation that promote vector acquisition and plant-to-plant transmission (Orlovskis et al. 2015). A comparison of vector transmission of plant viruses and bacteria is made in Table 1. More generally, microbes, including bacterial pathogens and viruses, affect plant–insect interactions in many ways (Simon et al. 2017) that affect both plant and pathogen fitness, as described later in this perspective.

THE CASE OF *XYLELLA FASTIDIOSA*

X. fastidiosa causes a "classic" plant disease, Pierce's disease of grapevine, in the sense that it has been known for more than a century, even though its etiology was elucidated much later. A personal account was given by Purcell (2013) of the progress made in the 20th century and the paradigm shifts in research that have occurred during this time, notably from the discovery of a bacterial causal agent, whereas the disease was previously assumed to be caused by a virus. Today, the disease continues to pose severe problems in the production of many food crops, notably perennial tree fruit, and has recently reemerged as global plant health threat through its incursion into Europe (Sicard et al. 2018). For every advance that has been made in understanding and managing the

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diseases caused, the pathogen has proved to be adaptable and continues to provide surprises as well as new insights in research. The literature on *X. fastidiosa* is extensive, with some 460 references retrieved between 2015 and June 2018 (EFSA 2018a). Historically, the diseases caused have been characterized by episodic invasions into new regions and hosts in the Americas and, most recently, into Europe. Saponari et al. (2017) provide the first experimental confirmation that *X. fastidiosa* is the causal agent of olive quick decline syndrome in Apulia, Italy, and the current situation in Europe was summarized by the European Food Safety Authority (EFSA 2018a). The future potential distribution of *X. fastidiosa* in Italy has been predicted using a MaxEnt distribution model (Bosso et al. 2016) and for the EU territory in relation to climate change by Godefroid et al. (2018). This perspective takes into account the most recent invasions into Europe but also future invasions, and proposes to set a framework for understanding the plant host–vector–*X. fastidiosa* interactions that lead to invasion.

The current state of the epidemiology of *Xylella fastidiosa* is comprehensive, with extensive literature citations given in the recent review by Sicard et al. (2018). The key feature of the diseases caused by *X. fastidiosa* is that its development in a host population is entirely dependent on plant-to-plant transmission by insect vectors, and encapsulates "the inseparable ecological trinity" of plant, vector, and pathogen developed by Walter Carter in the 1930s in the context of plant viruses (Carter 1939; Gutiérrez et al. 2013). The complication is that, for each component (host plant, bacterium, and vector), there is considerable diversity (EFSA 2018a). The bacterium has many subspecies and other infraspecific forms (EFSA 2018a; Sicard et al. 2018); the vectors are many and, in principle, include any xylem-feeding insect (Almeida et al. 2005). The host range is one of the widest for any plant pathogen but is eclipsed by the aphid-transmitted *Cucumber mosaic virus*, with more than 1,000 host plant species (Roossinck 2002) and includes both economic crops and plants in natural or unmanaged communities (EFSA 2018a,b). Even within subspecies, there can be host specialization (Nunney et al. 2013; Sanderlin 2017). There was a strong effect of strain variation arising from different hosts (Lopes et al. 2010). Multiplication rate of different strains affected symptom severity and bacterial persistence in alfalfa, with some strains dying out. Similarly, vector competence is associated with host species and strain variation (Lopes et al. 2009). Transmission efficiency can vary according to vector species, host species and cultivars, and *X. fastidiosa* strain (Almeida 2016). Given this diversity of strain variants, it is largely unknown whether coinfection of hosts leads to the types of interactions reported for some plant viruses which affect both transmission and establishment parameters (Blaisdell et al. 2015).

The vectors of *X. fastidiosa* are xylem-feeding insects and their biology in relation to disease epidemiology was reviewed by Redak et al. (2004). A particular aspect reviewed was the establishment and invasion by a new exotic sharpshooter vector in California Almeida and Purcell (2003). Although most diseases in the Americas occur on nonnative crop plants, the bacterium is considered to be endemic; hence, the increased threat to production was the consequence of an invasive and efficient exotic vector acquiring an endemic pathogen. The introduction of the invasive glassy-winged sharpshooter to California in the late 1980s (Stenger et al. 2010) eventually led to epidemics of oleander leaf scorch (Purcell et al. 1999) and Pierce's disease (Hopkins and Purcell 2002; Perring et al. 2001) in Southern California. By contrast, in Europe,

TABLE 1
Comparison of the mode of transmission for insect-transmitted bacteria and viruses[a]

Pathogen	Mode of transmission[b]	Vector latency	Loc	Insect vectors
Bacteria				
'*Candidatus* Phytoplasma'	CircProp	Days to months	P	Cicadomorpha (Leafhoppers, planthoppers), Stenorrhyncha (Psyllids)
Spiroplasma sp.	CircProp	Days to months	P	Cicadomorpha (Leafhoppers)
'*Ca.* Liberibacter' sp.	CircProp	Days to months	P	Stenorrhyncha (Psyllids)
Xylella sp.	NoncircProp	None	X	Cicadomorpha (Sharpshooters, Spittlebugs)
Viruses				
Cucumovirus, Potyvirus (many others)	Nonper	None	P, X?	Aphidomorpha (Aphids)
Closterovirus	Semiper	None	P	Aphidomorpha (Aphids)
Crinivirus, Ipomovirus	Semiper	None	P	Aleyrodoidea (Whiteflies)
Begomovirus	Circ	Hours to days	P	Aleyrodidea (Whiteflies)
Luteovirus, Polerovirus	Circ	Hours to days	P	Aphidomorpha (Aphids)
Curtovirus, Mastrevirus	Circ	Hours to days	P	Cicadomorpha (Leafhoppers)
Fijivirus, Phytoreovirus	CircProp	Days to months	P, X?	Cicadomorpha (Planthoppers)
Marafivirus	CircProp	Days to months	P	Cicadomorpha (Leafhoppers)
Rhabdovirus	CircProp	Days to months	P	Aphidomorpha (Aphids), Cicadomorpha (Leafhoppers, Planthoppers)
Tenuivirus	CircProp	Days to months	P	Cicadomorpha (Planthoppers)
Tospovirus	CircProp	Days to months	P	Thysanoptera (Thrips)

[a] Alternative transmission modes, mostly beetle transmissions of bacteria (e.g., *Pantoea stewartii*) or viruses, have not been included. In addition to similarities for some modes of transmission, vector latency, localization (Loc) (P = phloem and X = xylem), and insect vectors, the comparisons also point out some major differences. The table was elaborated based on data from Bragard et al. (2013), Dáder et al. (2017), and Orlovskis et al. (2015).

[b] CircProp = circulative propagative, NoncircProp = noncirculative propagative, Nonper = nonpersistent, Semiper = semipersistent, and Circ = circulative.

only a few sharpshooter species but high numbers of spittlebug species are present. Endemic spittlebugs, in particular the meadow spittlebug *Philaenus spumarius*, are vectors on olive in Italy (Cornara et al. 2017a,b). Although the role of *P. spumarius* as vector in Europe has been confirmed, other potential insect vectors such as *Neophilaenus campestris*, in association with different *X. fastidiosa* subspecies, remain a possibility. Surveys conducted in three regions of Spain showed the presence of spittlebugs, including *N. campestris*, as potential vectors but not the sharpshooter vectors found in the Americas (Lopes et al. 2014). *X. fastidiosa* has subsequently been reported in the Balearics and Alicante (EFSA 2018a). Thus, for Europe, up to now, the threat arises from an endemic vector acquiring and spreading an exotic and introduced pathogen.

The range of potential vectors is worrying in relation to future outbreaks and invasions. It is assumed that all xylem-feeding insects can be vectors (Almeida et al. 2005). Some 43 Auchenorrhyncha species were identified in studies on citrus variegated chlorosis in Argentina (Dellapé et al. 2016), some of which were dominant in citrus, others in surrounding vegetation, with each of the dominant species testing positive for *X. fastidiosa* using molecular detection methods. Bacterial populations in the meadow spittlebug were one to two orders of magnitude smaller than those typically found in Cicadellidae vectors but there was a direct relationship between numbers and transmission to plants (Cornara et al. 2016). Seasonal abundance of insect vectors has been reported in the United States and Europe (Ben Moussa et al. 2016; Overall and Rebek 2015). Puerto Rico is currently free of *X. fastidiosa* but populations of potential Cicadellidae vectors were monitored in coffee and citrus, both susceptible hosts (Brodbeck et al. 2017). One potential vector species was found in coffee and an associated shade host but none on citrus. Despite these complexities, there is a need to consider each component—bacterium, vector, and host plant—and their interactions in epidemiological analysis to inform disease control strategies such as those reviewed by Overall and Rebek (2017).

In terms of introduction into Europe, although *X. fastidiosa* was detected for the first time in 2013, in-depth analysis of datasets based on positive polymerase chain reaction (PCR) samples from the French Department Corse-du-Sud, by inferring pathogen dynamics form temporal count data, by Soubeyrand et al. (2018) suggest that the introduction might have occurred as early as in the 1980s. In terms of environmental factors, those related to soil, nutrition, and soil–water relationships and their interactions played a significant role in the expression of Pierce's disease in grapevine, possibly through effects on constitutive or induced resistance which might be exploited in disease management (Costello et al. 2017). Climax modeling was used to show that *X. fastidiosa* and vectors could survive in much of the coastal regions of Australia, that much of the native flora was also vulnerable, and, thus, that preparedness for such an incursion would be necessary (Rathé et al. 2012). Similarly, the impacts of *X. fastidiosa* on yield, tree performance, and longevity (Sisterson et al. 2012) are noted but not considered further.

Although we appreciate the paradigm shift from supposed virus to demonstrated bacterium as commented on by Purcell (2013), in our view, the framework described in this perspective is applicable to all vectored plant diseases and, as such, could be developed further as a new paradigm shift. We fully appreciate that, as a consequence, this perspective does not cover all the ways in which the epidemiology of *X. fastidiosa* can be investigated; notably, the pathways that may lead to the introduction and spread of the pathogen into a new region, country, or continent; and the influence of environmental factors on establishment, factors which have become important in the last decade in Europe (EFSA 2018a). Thus, the main question raised in this perspective is the extent to which research on the epidemiology of vectored plant virus diseases is applicable to vectored bacterial diseases, in particular those caused by *X. fastidiosa*. In so doing, we will use a modeling framework developed for plant–virus–vector interactions, noting both the similarities and differences.

The purpose of this perspective is not to model diseases caused by the genus *Xylella* and its many complexities but to present a "point of view" (= perspective) on a simplified modeling framework which could be adapted and made specific to a particular set of circumstances. The perspective is also not aimed specifically at mathematical modelers but at plant disease epidemiologists more generally, to make them more aware of an approach that has been found useful in plant virus epidemiology and, more generally, with vector-borne diseases of animals and humans. We would argue that convincing plant disease epidemiologists of the value of looking at insect-transmitted plant diseases is both useful and novel, because most plant disease epidemiologists do not deal with such diseases. The main points and message made are as follows.

i. A common approach to modeling insect-transmitted plant diseases can be formulated regardless of the pathogen taxa.
ii. This framework emphasizes the key role of transmission in determining disease dynamics, especially during the early stages of invasion, while recognizing that other approaches, especially concerning disease spread, are essential.
iii. The complexities of *Xylella* epidemiology can be incorporated into the framework depending on the modeling objectives.

A FRAMEWORK FOR MODELING *X. FASTIDIOSA* EPIDEMIOLOGY

For *X. fastidiosa* epidemiology, models have been proposed, mostly concerned with spread but with the vector considered only implicitly. Spatial analysis in almond orchards showed a mainly aggregated pattern of disease, with some influence on the pattern by susceptible cultivars (Groves et al. 2005). Park et al. (2011) investigated the relationship between Pierce's disease incidence and occurrence with the surrounding environment, providing useful spatial information on the disease in vineyards. Spatial and spatiotemporal models are valid in their own right, and certainly in terms of disease expansion following initial invasion and establishment. These models are essential in determining the strategies that can be taken to constrain further spread, and some articles do focus on such approaches. An explicit spatially dependent simulation model was developed and used to analyze the spread of disease affecting olive in Apulia, Italy, and the potential efficacy of control measures (White et al. 2017). The model outputs showed the importance of long-distance jumps in vector movement, the importance of extending buffer zones, and the significant role of nonolive vegetation in increasing the rate of spread. An epidemiological approach to gearing disease surveillance to control interventions is given by Parnell et al. (2017). Risk-based control based on epidemiological information and a spatial mathematical model suggests that the use of a variable radius outperforms a strategy of constant-radius removal of infected plants (Hyatt-Twynam et al. 2017; Vicent and Blasco 2017). One approach, implicitly spatial, that can be taken is the use of network models to assess the risks of the movement of pathogens in plant trade (Jeger et al. 2007), certainly applicable to *Xylella* spp., but this is a very broad area that goes beyond the scope of this perspective. However, network analysis suggests that attempts to eradicate the disease from southern Italy are futile and this region will provide a pathogen reservoir for further spread (Strona et al. 2017), a suggestion which appears contrary to the current EU emergency legislation (EFSA 2018a).

Most attempts to model or analyze spatial spread of *X. fastidiosa* stress insect dispersal capacities and extrapolating empirical data on disease gradients rather than modeling the essential features of the

vector–plant–bacterium interaction (i.e., transmission). As an exception to the lack of consideration of the vector, the role of seasonality in the epidemiology of *X. fastidiosa* in terms of vector abundance, infectivity, and host infection dynamics was modeled by Gruber and Daugherty (2013). Accounting for seasonal variability could lead to an eightfold reduction in within- and between-season disease spread. Seasonality is a topic we return to later in this perspective.

Theoretical models and invasion criteria. One approach to analyzing plant virus epidemics has been through the use of theoretical mathematical models (Jeger et al. 2018) which deal with the overriding importance of transmission mechanisms in determining epidemic dynamics (Jeger et al. 1998; Jeger et al. 2004; Madden et al. 2000). A linked ordinary differential equation approach has been used in most attempts to model the dynamics of a disease, certainly in terms of whether invasion is likely. Models come in various forms, covering only temporal dynamics of the disease or, in some cases, combining both temporal and spatial elements. In many models, the vector is included only implicitly or, in an increasing number of cases, can be incorporated explicitly. In the simplest nonspatial case, a single virus transmitted by a single vector infecting one host species is modeled and stresses the importance of transmission in epidemic processes.

Often the vector and host populations are assumed to be of constant size. Extensions can be made for more than one virus coinfecting a plant, the role of weeds or other vegetation in serving as a virus reservoir, and where multiple vectors are involved in transmission (van den Bosch and Jeger 2017). Models can even prove useful where there is little information on a putative pathogen and assumed potential vectors but where the disease caused is well characterized (Cunniffe et al. 2014). In the simplest case referred to above of one virus, one vector, and one host plant, the dynamics of a vectored plant disease was modeled by a system of linked differential equations, the so-called susceptible-exposed-infectious-removed (SEIR) model, combined with a similar partitioning of the vector population into nonviruliferous (X), latent (carrying the virus but not yet inoculative) (Y), and inoculative (Z) categories. Full details are provided by Jeger et al. (2004) and references therein by the authors, where the full system of equations with some variation in notation is given. A schematic of the SEIR-vector model is shown as Figure 3 in Jeger et al. (2018). The parameters defined in the system of equations are described in Table 2. As with any model, a number of simplifying assumptions are made. The host and pathogen populations are assumed to be constant. In the case of the host, the reasonable assumption is made that replanting is practiced to replace dead trees (or those removed or rogued because of disease). The vector population is assumed to be constant, not necessarily at carrying capacity, with immigrants replacing those that die or emigrate. This assumption is more problematic and open to challenge. In the original articles, there were additional parameters describing vertical transfer to vector progeny, which is not relevant for *X. fastidiosa* (Freitag 1951), and also explicit immigration and emigration terms; however, these are not considered here. Using standard mathematical techniques for analyzing this system of equations, an expression can be derived in terms of the model parameters. The expression takes the form of a threshold which determines whether or not the virus can invade and persist in a healthy host population and, as a corollary, the extent of disease control practices necessary to prevent this happening.

The invasion criterion is written in words which heuristically follow the sequence of biological events from the introduction of a single viruliferous vector into an otherwise nonviruliferous vector population residing in a healthy plant population. The point of writing the invasion criterion in words is for the benefit of the nonmathematical plant disease epidemiologist. For the interested reader, the background equations and an illustrative figure are shown in the publications cited above (Jeger et al. 2004, 2018). The parameter combinations corresponding to these terms are given in Table 3, together with the full invasion criterion, are as follows.

Number of plants that become infected (E) (the exposed class) = probability that an introduced viruliferous vector becomes inoculative × feeding time per vector per day × inoculation rate × average time an inoculative vector remains inoculative

Of these infected plants, the number that become infectious (I) (the infectious class) = E × probability an infected plant becomes infectious

Number of nonviruliferous vectors that acquire virus from infectious plants (Z) (the inoculative class) = I × vectors per plant × feeding time per vector per day × acquisition rate × the average time an infectious plant remains infectious

Thus, starting with one viruliferous vector, if the invasion criterion is greater than 1 (i.e., the resulting number of vectors that become inoculative is greater than 1), then the virus can invade the host population. If the invasion criterion is less than 1, then the virus cannot establish. A similar heuristic argument can be made for the case where the initial infected unit is an infected plant planted into an otherwise healthy plant population.

This invasion criterion is related to a more rigorous but often less intuitive parameter, the basic reproduction number R_0 for a vectored plant disease (Shi et al. 2014), whose numerical value gives the exact number of secondary infected units arising from the introduction of one primary infected unit into an otherwise healthy population. In principle, the basic reproduction number can be extended to the case where there are multiple vector species, situations where competition between vectors is occurring, and vector control through insecticides is practiced (van den Bosch and Jeger 2017). R_0 can also be used to give an approximation to the

TABLE 2
List of model parameters and their description as defined in a simple susceptible-exposed-infectious-removed (SEIR) model of a vectored plant virus disease

Parameter	Description
Host	
K	Population size (constant)
β	Mortality rate (turnover rate)
γ^{-1}	Plant latent period[a]
ζ^{-1}	Infectious period[b]
Vector	
P	Population size (constant)
α	Death rate (= birth rate)
η^{-1}	Vector latent period[a]
τ^{-1}	Infectious period[b]
Transmission	
T	Time spent feeding per visit
φ	Plants visited per vector per unit time
λ_1	Inoculation rate[c]
λ_2	Acquisition rate[d]

[a] Defined as the reciprocal of rate at which an infected plant or viruliferous vector becomes infectious or inoculative.
[b] Defined as the reciprocal of the rate at which an infectious plant or inoculative vector loses infectiousness or ability to inoculate.
[c] Can be estimated from the inoculation access periods (Madden et al. 2000).
[d] Can be estimated from the acquisition access periods (Madden et al. 2000).

initial rate of disease increase (Madden et al. 2000), an important parameter which indicates the speed at which the early epidemic develops, although additional model assumptions can affect the consistency of estimates (Roberts and Heesterbeek 2007).

In the model framework proposed, the vector (and host) population density is assumed to be constant. This assumption can hold approximately if the rates of increase and decrease are slow relative to the rates of acquisition and inoculation in the transmission process. The invasion criterion, written in words above, is derived directly from the underlying ordinary differential equations at the disease-free state, where the respective populations are constant. We note that this does not give the true R_0, which would be calculated by the Next Generation Matrix method (van den Bosch and Jeger 2017). It is also the case that derivation of R_0 is problematic when there is seasonality in any of the transmission parameters or host or vector population densities. However, there is theoretical work which shows how periodicities in the host (Wesley and Allen 2009) and vector (Bacaër 2007) populations can be taken into account to derive, in effect, an average R_0. For *X. fastidiosa*, a number of studies have indicated the role of seasonality in determining disease development. Seasonal variability in the vector population could lead to an eightfold reduction in within- and between-season disease spread (Gruber and Daugherty 2013). Plants inoculated late in the growing season are more likely to cure during the winter than plants inoculated early in the season (Cao et al. 2011; Feil et al. 2003; Lieth et al. 2011). Accordingly, there appears to be important seasonal effects on pathogen dynamics. This would, in principle, affect the way in which the transitions between states in the SEIR model are specified; for example, perhaps as a return transition from the infectious to the exposed (or possibly susceptible) class.

Despite these qualifications, the main utility of the proposed approach is that it enables the plant, virus, and vector components of an epidemic, and their interactions, to be integrated into a single model framework and their relative contribution to epidemic development assessed. Numerical analysis of the model above showed that vector abundance, activity, and behavior, in relation to transmission, are important determinants of disease dynamics (Jeger et al. 2004), and we take up these elements below in relation to *X. fastidiosa*. We also note that there are examples of recent modeling studies in which this type of framework has been used to answer strategic questions concerning epidemiology and deployment of host resistance and other disease control strategies and, in doing so, have addressed issues relevant for *X. fastidiosa* management (Kyrkou et al. 2018; Sisterson and Stenger 2018).

TABLE 3
Derived terms and their interpretation in the invasion criterion obtained for a simple susceptible-exposed-infectious-removed (SEIR) model of a vectored plant virus disease as described heuristically in the text

Term in invasion criterion	In symbols[a]
Probability a viruliferous vector becomes inoculative $\eta/(\eta + \alpha)$	$\eta/(\eta + \alpha)$
Feeding time per inoculative vector per unit time × inoculation rate	$\lambda_1\Phi T$
Average time an inoculative vector stays inoculative	$1/(\tau + \alpha)$
Probability that an infected plant becomes infectious	$\gamma/(\gamma + \beta)$
Feeding time per nonviruliferous vector per unit time × acquisition rate	$\lambda_2\Phi T$
Average time an infectious plant remains infectious	$1/(\zeta + \beta)$
Vectors per plant	P/K

[a] Symbols: η = rate at which a viruliferous vector becomes inoculative, α = death rate (birth rate), λ_1 = inoculation rate, T = time spent feeding per visit, γ = rate at which an infected plant becomes infectious, β = mortality rate (turnover rate), λ_2 = acquisition rate, τ = rate at which an inoculative vector loses the ability to inoculate, ζ = rate at which an infectious plant loses infectiousness, P = vector population size (constant), and K = host population size (constant). The invasion criterion is the product of these terms: $\eta/(\eta + \alpha) \times \lambda_1\Phi T \times 1/(\tau + \alpha) \times \gamma/(\gamma + \beta) \times \lambda_2\Phi T \times P/K \times 1/(\zeta + \beta)$. If the criterion has a value > 1, then the disease will invade.

Application and relevance for *X. fastidiosa*. The framework developed here allows an invasion criterion to be specified for which some if not all of the parameters are known for some vector–host–*X. fastidiosa* combinations. The question then arises as to whether this approach is applicable to *X. fastidiosa*, given the complexities noted above related to plant–bacterium–vector interaction. As already stated, we do not propose a specific model for diseases caused by *X. fastidiosa* but, rather, a modeling approach which includes the key epidemiological parameters influencing the initial invasion of disease and which, because of its simplicity, can be adapted for different purposes. The composite parameters that determine whether or not a disease can invade and establish (Table 3) in a new location are common to all diseases caused by *X. fastidiosa*. We argue that their epidemiology represents variations on a common theme. The problem is more in how new manifestations of disease can occur in the future and whether or not these are predictable.

First, we substitute "bacteriferous" for viruliferous. Second, we note that the bacterium is restricted to the xylem, and transmission can only occur with xylem-feeding insects, unlike the case with most viruses (and other insect-borne bacteria), where transmission is from the phloem (Table 1). In our view, this fact does not fundamentally affect the applicability of the framework developed for viruses. Many viruses can occur and move systemically in the xylem as well as the phloem but often it is not clear whether transmission by insects occurs from or to the xylem. Dáder et al. (2017) report transmission occasionally to the xylem for species of *Alfomovirus*, *Caulimovirus*, *Cucumovirus*, *Crinivirus*, *Potyvirus*, and *Waikavirus*, all noncirculative viruses. Phytoreovirus-like sequences have been isolated from the salivary glands of the xylem-feeding *Homalodisca vitripennis* (Katsar et al. 2007). *Turnip mosaic virus* can move systemically through the phloem and the xylem (Wan et al. 2015). For some leafhoppers such as *Circulifer tenellus*, ingestion of both phloem and xylem is necessary to obtain high rates of ingestion (Stafford and Walker 2009; Stafford et al. 2012). As noted by Novotny and Wilson (1997), the evolutionary transitions from phloem to xylem feeding in species of the order Hemiptera may place an energetic constraint on the minimum insect body size.

At this point in time, the modeling approach described has not been followed for *Xylella* spp.-incited diseases. In this perspective, we now look at the various components involved in the dynamics of a vectored plant disease, as summarized in Table 3, and consider their relevance to *Xylella* spp. epidemiology. Due to the many hosts and infraspecific variation in *X. fastidiosa*, the lengths of the plant latent periods have been estimated for only a few crops. The time to symptom development following insect inoculation is highly variable for several crops (Hill and Purcell 1995; Lopes et al. 2005; Saponari et al. 2016), ranging from days to more than 1 year; however, less is known in the field under natural infection. Recently, it has been shown that previsual-symptom detection of infection is possible in olive through airborne imaging of plant functional traits (Zarco-Tejada et al. 2018). However, the key epidemiological parameter is not the time to symptoms but the plant latent period (i.e., the time from infection to acquisition by the vector, whether from systemic or localized infection) (Hill and Purcell 1995). This parameter was investigated by Hill and Purcell (1997) but very

much depends on the host plant–vector system investigated. A diseased tree, once infectious, is likely to remain infectious so long as the xylem remains functional and vectors continue to feed. Acquisition rate may vary according to disease progress on an individual tree. The model basically assumes that transitions from the infectious to the removed class have exponential distributions, thus giving an estimate of the mean infectious period. There are ways of incorporating different assumptions on these transitions but, again, these are beyond the scope of this perspective.

There is more information on at least some vectors, as described below, but vector activity within a crop population is largely unexplored. It is also the case that, following acquisition, the bacterium is restricted to the foregut (Almeida et al. 2005) and, hence, the vector latent period (before inoculation) would be very short or nonexistent (Almeida et al. 2005) and yet the bacterium multiplies there, presumably for the life of the vector. Therefore, *X. fastidiosa* corresponds to a noncirculative propagative bacterium, a case not described for persistent plant viruses, where movement from the foregut to the hemocyl and to the salivary glands would be the norm, leading to an extended vector latent period. We note also that the terminology used for plant virus vector transmission can have a different interpretation for those working with *X. fastidiosa* vectors. Bragard et al. (2013) made an attempt to systematically review all of the virus vectors, with three time-dependent figures: one for acquisition, another one for retention, and a final one for inoculation. Killiny and Almeida (2013) proposed similar steps for their detailed study of the interaction of *X. fastidiosa* with its vectors. Studies have mostly focused on acquisition access period and inoculation access period but it has proved difficult to provide a very clear picture from experimental studies, probably because of high variation depending on the host plant, conditions, level of bacteria in the plants, and so on. This being said, if we follow Almeida et al. (2005), acquisition is almost immediate after feeding, there is no latency between acquisition and ability to inoculate (although vector residence times and behavior would affect this), retention is over the whole life of the adult or nymphs (but without transstadial passaging), and inoculation would continue with the life of the insect stage considered.

VECTOR POPULATION ABUNDANCE AND ACTIVITY

The population abundance of vectors (scaled by the number of host plants) is one component of the invasion criterion. Although aspects of the dynamics of insect-transmitted pathogens such as *X. fastidiosa* are related to vector abundance, many aspects of vector reproductive biology are poorly understood. Key nutritional factors involved in glassy-winged sharpshooter egg production and, hence, population growth are described by Sisterson et al. (2017). Although Sisterson et al. (2017) demonstrated that adult diet affects glassy-winged sharpshooter egg production and, hence, rates of population growth, key nutritional factors affecting egg maturation remain to be determined. Thus, there is a greater need to study vector reproduction biology and mortality to better understand population growth and disease spread (Sisterson and Stenger 2016; Sisterson et al. 2018).

A key question is the effectiveness of vector control in *X. fastidiosa* epidemiology. The dynamics of the glassy-winged sharpshooter were monitored in citrus, grapevine, and stone fruit in the San Joaquin valley in California before and after a control program was introduced (Park et al. 2006). The low numbers of vectors following spray treatment make it unlikely that statistically significant relationships with disease could be found in the different crops at the spatial scale considered. Monitoring of vectors in different agricultural crops and alfalfa fields subject to different management, including insecticide treatments, was made over 14 months in California (Wistrom et al. 2010). Recommendations on vector control to reduce vector populations and inoculum presence were made. However, vector control using insecticides reduced vector populations but had little effect on disease prevalence (Daugherty et al. 2015). The spread of disease may be reduced but the effect seems highly dependent on past history in the vineyard and may take a number of seasons to become apparent. The relatively small effect on disease prevalence was attributable, in part, to low regional vector population levels arising from area-wide control programs.

Winged adults, because of their high mobility and persistent association with the bacterium, are mostly responsible for *X. fastidiosa* spread. Vector activity within and between crops is another component of the invasion criterion. Spread can be predominantly from alternative crops to grapevine or from grapevine to grapevine in California, depending on the season (Hopkins and Purcell 2002), or exclusively from citrus to citrus in Brazil, regardless of the presence of orchard weeds known to harbor the bacterium. Vector movement to grapevine from adjacent citrus plantings under different irrigation treatments in California was monitored and net dispersal rates calculated (Krugner et al. 2012). There appeared to be an element of random rather than oriented movement, perhaps indicating an inability of the vector to respond to long-distance visual or olfactory cues (Patt and Sétamou 2007). With the introduction of the invasive glassy-winged sharpshooter, the vector overwintered on citrus, reaching large populations of 1 to 2 million sharpshooters/ha moving subsequently to adjacent grapevine (Coviella et al. 2006). Together with Blua and Morgan (2003), these two articles provide almost the only published information available for within-crop activity of vectors and movement from plant to plant.

There is much less information available on the population abundance of *Philaenus spumarious* in Europe. It is anticipated that much information will become available on the population abundance of this confirmed vector of *X. fastidiosa* in Mediterranean olive groves as part of an EFSA procurement project ("Collection of data and information on biology and control of vectors of *X. fastidiosa*"). This study is collecting data on nymph densities at different sites. At the site with highest population densities, there were averages of 21 and 30 nymphs/m^2 in 2016 and 2017, respectively (EFSA 2018a).

VECTOR TRANSMISSION

Acquisition rate and inoculation rate are important determinants of vector-borne disease dynamics. Transmission in terms of acquisition and inoculation of *X. fastidiosa* by vectors has been the subject of many studies, both qualitative and quantitative. Chatterjee et al. (2008) contrasted the biology of the bacterium in the plant and in the vector, contrasting the traits that determine movement within the plant with those governing acquisition and inoculation by the sharpshooter vectors. Daugherty and Almeida (2009) estimated these parameters for two vectors, one native and one invasive, of *X. fastidiosa* in grapevine, and also showed the dependence of transmission on temperature. These estimates effectively decoupled vector numbers from acquisition and showed large differences in the transmission efficiency of the two vectors. It seems logical to suppose that acquisition efficiency would be related to the bacterial populations in the plant and that low bacterial populations would serve as an inefficient reservoir for acquisition (Almeida et al. 2005). However, Rashed et al. (2011) found no significant relationship between grapevine cultivar susceptibility to *X. fastidiosa* expressed as bacterial populations in petioles and transmission efficiency from these plants, although innate vector preferences for different cultivars may have confounded the relationship. Because the bacterium is restricted to the foregut (Purcell and Finlay 1979), the number of bacterial cells per insect is low. However, very few live bacterial cells in the vector's foregut are required for transmission (Hill and Purcell 1995). At the moment,

the size of the within-plant bacterial population is not a component in the overall invasion criterion derived above. Indeed, this mirrors the case where within-plant virus titer has rarely been included in models of plant virus transmission (Jeger et al. 2018).

It has been shown that host physiological state can affect transmission independently of host susceptibility and the preference of *X. fastidiosa* vectors for asymptomatic hosts. The effect of water stress on transmission to citrus and almond by the glassy-winged sharpshooter in California was studied in the laboratory by Krugner and Backus (2014). Acquisition and inoculation events following extended feeding were observed only in fully irrigated plants, suggesting that reduced irrigation may help to reduce vector numbers and transmission efficiency. Host–vector specificity in transmission is often reported. In Italy, field-collected meadow spittlebugs were shown to transmit *X. fastidiosa* in inoculation tests to a range of test plants but not grapevine (Cornara et al. 2017b). More generally, specificity of host–pathogen–vector interactions, arising from the diversity present in each component, is an important aspect of *X. fastidiosa* transmission and epidemiology (Lopes et al. 2009) that should be considered in designing disease management strategies. Studies were conducted to investigate whether transmission could be blocked or reduced by the use of peptides which inhibit cell adhesion by insects, opening up new directions for disease control (Labroussaa et al. 2016).

NEW DIRECTIONS IN HOST–VECTOR–PATHOGEN INTERACTIONS

Recent research has opened up many new areas relevant for the epidemiology of vectored plant diseases. A general review of how pathogen–plant–vector interactions affect transmission and, hence, disease spread of vectored plant diseases is given by Eigenbrode et al. (2018). In particular, the phenomenon of conditional vector preference, whereby preference for healthy or infected plants is dependent upon the status of the vector (i.e., viruliferous or nonviruliferous), has been investigated experimentally (Rajabaskar et al. 2014) and modeled (Roosien et al. 2013). Host–vector interactions can be adaptive, as shown for many plant viruses and, to a lesser extent, with phytoplasmas and insect-transmitted bacteria. For example, with the vector-borne stolbur phytoplasma, the host shift from ancestral hosts to new hosts can lead to vector adaption in terms of survival related to the infection status of the hosts (Maixner et al. 2014). The psyllid vector of '*Candidatus* Liberibacter asiaticus' was attracted initially to diseased citrus but, after feeding, preferentially moved to healthy plants, a behavior that enhances pathogen spread but was not affected by whether the vector was carrying the pathogen (Mann et al. 2012).

TABLE 4
Additional parameters applicable for cases where vector preference for healthy or diseased plants can be expressed quantitatively

Parameter[a]	Description
ν (with $0 \leq \nu < \infty$)	Degree to which a vector prefers to land and feed on an infected plant: if $\nu = 1$, preference is equal for infected and healthy plants and host selection is given by the relative frequencies of each plant class
$S/(S + \nu I)$	Probability that a vector chooses to land and feed on a healthy plant: if $\nu = 0$, vectors only land and feed on healthy plants and no acquisition occurs[b]
$\nu I/(S + \nu I)$	Probability that a vector chooses to land and feed on an infected plant: for $\nu \to \infty$, vectors only land and feed on infected plants and no inoculation occurs[b]

[a] Symbols: ν = vector preference, S = healthy and susceptible plant population density, and I = infected and infectious plant population density.
[b] The formulation is such that the probabilities sum to 1.

The simple SEIR and vector model described by Jeger et al. (2004) makes a number of assumptions concerning the parameters defined and, hence, the criterion for invasion. As with all models, the assumptions made can be challenged. Vector birth and death rates are considered as constants and unaffected by whether the vector has acquired the pathogen, an assumption that does not capture the full impacts on vector populations and disease incidence (Sisterson 2009). Similarly, vector behavior in terms of landing and feeding preferences is assumed to be unaffected by whether the host is healthy, asymptomatic, or symptomatic; and whether these preferences are affected by whether the vector is viruliferous or nonviruliferous (i.e., whether vector preference is conditional). Such vector preferences can be included in the model framework above by including a preference parameter that denotes the degree to which a vector prefers to land and feed on an infected plant. The probabilities that a vector chooses to land and feed on a healthy or infected plant can then be defined according to the frequency of each plant category in the population (Table 4). In the case of *X. fastidiosa*, vector preference is reported to be for healthy or at least asymptomatic plants (i.e., the preference parameter is less than 1). These frequency-dependent choices were used in a model of malarial transmission (Chamchod and Britton 2011) (N. J. Cunniffe, personal communication), emphasizing the commonality in approach possible across vector-borne diseases of humans, animals, and plants. In a different context, this frequency-dependent representation of choice has been used for farmers' selection of healthy or virus-infected vegetative cuttings for replanting (Holt et al. 1997).

Mauck et al. (2016) distinguishes between host-dependent vector preference and conditional vector preference dependent on infected versus healthy host status. In a mathematical model, Shaw et al. (2017) showed that vector population dynamics and dispersal and conditional preferences are both important for rates of virus spread. Zeilinger and Daugherty (2014) examined the effects of host defense mechanisms and vector preference on disease dynamics. They found that resistance mechanisms were generally effective regardless of vector preference, whereas the consequences of tolerance depended on vector preference. The implications of vector preference for disease control remain largely unexplored.

Such considerations have come to prominence in recent years and the implications for diseases incited by *X. fastidiosa* need to be investigated, with the model framework described above refined accordingly. Host factors such as carbohydrate structures may modulate gene expression and facilitate vector transmission (Killiny and Almeida 2009). Citrus variegated chlorosis-infected plants were less favored hosts than uninfected or asymptomatic plants, suggesting that asymptomatic plants may be more important sources of infection than infected plants (De Miranda et al. 2013). Three sharpshooter vectors showed preference for healthy or asymptomatic grapevines in laboratory choice experiments and also in field trials (Daugherty et al. 2011). This feeding behavior would likely affect the probability of acquisition unless acquisition efficiency was high on asymptomatic vines. Sharpshooter vectors of citrus variegated chlorosis preferred healthy over symptomatic citrus plants in choice experiments in observation chambers but showed no preference between healthy and asymptomatic plants (Marucci et al. 2005). However, for those sharpshooters that initially chose the symptomatic plants, they gradually moved to healthy plants over a 48-h period; whether this was a switch in preference due to acquiring the bacterium is unknown. Provided that the period of time necessary for acquisition was short and acquisition efficiency high, this may favor disease spread in the field. This seems to be the case for grapevine (Purcell and Finlay

1979) but not citrus (Krugner et al. 2000; Marucci et al. 2003). When confined to infected plants, there was a reduction in feeding on symptomatic but not on asymptomatic plants (Marucci et al. 2005). These results suggest that early asymptomatic infections may be an effective source of *X. fastidiosa* for subsequent disease spread. At the present time, there seems to be no direct evidence that vector preference for diseased or healthy hosts is conditional upon whether the vector has acquired the bacterium.

CONCLUSIONS

This perspective aims to show that insect-transmitted diseases have many features in common regardless of whether the causal pathogen is a bacterium, phytoplasma, or virus. A model framework can be developed that encapsulates the essential interactions between the pathogen, plant, and insect vector in terms of key epidemiological parameters, from which a criterion can be developed that determines whether the pathogen would establish, persist, and lead to an epidemic in a host population. As has been pointed out by many workers, *X. fastidiosa* induces complex diseases with much infraspecific variation in the bacterium; an extensive host range, including both economic crops and natural vegetation; and a multitude of potential xylem-feeding insect vectors. Given this complexity, it is understandable why individual components specific to a particular system have been researched. However, especially in cases where new outbreaks occur such as the recent invasions into Italy, France, and Spain, it is important that the multilevel interactions between the range of *X. fastidiosa* subspecies, hosts species, and (currently) restricted number of known vectors are investigated in a holistic way. The model framework developed in this perspective, although in many ways simplistic, is one approach that can be taken. Where the parameter values can be estimated for a specific system, then their relative importance in determining whether an incursion or isolated outbreak will lead to a full-blown epidemic in time and space can be assessed.

For *X. fastidiosa*, there are some basic gaps in knowledge and elements that need to be incorporated in the simple framework presented.

1. For a given host what is the relationship between bacterial development and time to symptoms, and the ability of a (given) vector to acquire the bacterium?
2. What is the basis for vector preference for healthy or asymptomatic plants, and is this affected in any way by whether the vector carries the bacterium?
3. Does bacterial multiplication in the foregut affect in any way vector life history, behavior, and activity, or modulate inoculation efficiency? (It is well known that insect endosymbionts play a major role in providing the insect with amino acids lacking in the insect diet; especially for xylem-feeding insects, the challenge is a major one as compared with phloem-feeding insects.)
4. How important is seasonality for vector abundance and activity and what is the best way to incorporate this?
5. Could coinfection with bacterial variants in the plant or in the vector affect transmission in ways reported for plant viruses?
6. Can the phenomenon of overwintering curing effect be generalized to hosts other than grapevine and incorporated into the framework through seasonal effects on transmission and vector parameters?

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