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Mathematical models are a powerful method to understand and control the spread of Huanglongbing

Rachel A Taylor, Erin Mordecai, Christopher A Gilligan, Jason R Rohr, Leah R Johnson

Huanglongbing, or citrus greening, is a global citrus disease occurring in almost all citrus growing regions and causing substantial economic burdens to individual growers, citrus industries and governments. Successful management strategies to reduce disease burden are desperately needed but with so many possible interventions and combinations thereof, it is difficult to know which are worthwhile or cost-effective. We review how mathematical models have yielded useful insights into controlling disease spread for other vector-borne plant diseases, and the small number of mathematical models of Huanglongbing. We adapt a malaria model to Huanglongbing, by including temperature-dependent psyllid traits and economic costs, to show how models can be used to highlight which parameters require more data collection or which should be targeted for intervention. We analyze the most common intervention strategy, insecticide spraying, to determine the most cost-effective spraying strategy. We found that fecundity and feeding rate of the vector require more experimental data collection, for wider temperatures ranges. The best strategy for insecticide intervention was to spray for more days rather than pay extra for a more efficient spray. We conclude that mathematical models are able to provide useful recommendations for managing Huanglongbing spread.

1 **Mathematical models are a powerful**
2 **method to understand and control the**
3 **spread of Huanglongbing**

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9 **ABSTRACT**

10 Huanglongbing, or citrus greening, is a global citrus disease occurring in almost all citrus growing regions
11 and causing substantial economic burdens to individual growers, citrus industries and governments.
12 Successful management strategies to reduce disease burden are desperately needed but with so many
13 possible interventions and combinations thereof, it is difficult to know which are worthwhile or cost-effective.
14 We review how mathematical models have yielded useful insights into controlling disease spread for
15 other vector-borne plant diseases, and the small number of mathematical models of Huanglongbing. We
16 adapt a malaria model to Huanglongbing, by including temperature-dependent psyllid traits and economic
17 costs, to show how models can be used to highlight which parameters require more data collection or
18 which should be targeted for intervention. We analyze the most common intervention strategy, insecticide
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20 rate of the vector require more experimental data collection, for wider temperatures ranges. The best
21 strategy for insecticide intervention was to spray for more days rather than pay extra for a more efficient
22 spray. We conclude that mathematical models are able to provide useful recommendations for managing
23 Huanglongbing spread.

24 **Keywords:** Citrus Greening, sensitivity analysis, intervention strategies, insecticide, mathematical
25 modeling, vector-borne disease

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33 INTRODUCTION

34 Huanglongbing (HLB), also known as citrus greening disease, is a devastating citrus disease native to
35 Asia (Bové, 2006; Gottwald, 2010; Hall et al., 2013) but now exists in virtually all citrus-growing regions
36 (Narouei-Khandan et al., 2015). In the last 10 years, it invaded the Western Hemisphere, primarily Brazil
37 and Florida, where it has spread rapidly and caused extensive economic burdens (Hodges and Spreen,
38 2012; Spreen et al., 2006). HLB is caused by three bacteria: *Candidatus Liberibacter asiaticus* (CLas),
39 *Candidatus Liberibacter africanus*, and *Candidatus Liberibacter americanus*. The Asian citrus psyllid
40 (ACP), *Diaphorina citri* Kuwayama is the primary vector (Grafton-Cardwell et al., 2013). The disease
41 causes chlorosis of leaves, dieback and in severe cases, tree death. Infected trees develop fruit that is of
42 poor quality and drops early, reducing yields of edible and marketable fruit from diseased trees (Bové,
43 2006). HLB is undermining the viability of an important international industry, and possibly endangering
44 the persistence of multiple species of citrus (Hall et al., 2013).

45 Intervention strategies for Citrus Greening

46 Nowhere in the world is citrus greening under adequate control (Gottwald, 2010; Hall et al., 2013). The
47 process of finding effective intervention strategies has been challenging, at least partly because of the
48 difficulties in determining the infection status of trees and the long duration before trees show symptoms
49 (Manjunath et al., 2008; Gottwald, 2010). The current state of control involves insecticide spraying to
50 reduce the abundance of Asian citrus psyllid (Grafton-Cardwell et al., 2013).

51 To fight citrus greening disease, new intervention strategies are needed. This could be by developing
52 new controls or by combining current and new controls into an optimal strategy (Halbert and Manjunath,
53 2004; Wang and Trivedi, 2013). However, before they can be implemented in the field they need to
54 be tested for efficacy. There are presently tens if not hundreds of hypothetical interventions that could
55 be tested, such as antibiotics (Zhang et al., 2014), pesticides (Qureshi et al., 2014), biocontrol agents
56 (Michaud, 2002), heat treatment (Hoffman et al., 2013), new tolerant or resistant tree stocks (Dutt et al.,
57 2015), nutrient additions (Gottwald et al., 2012), tree removal (Gottwald, 2010), changes to tree spacing
58 (Martini et al., 2015), intercropping (Gottwald et al., 2014), psyllid deterrents and barriers (Tisgratog et al.,
59 2016; Tomaseto et al., 2016), etc., and even more daunting are the different factorial combinations of
60 interventions to test. It would be impossible and costly to test this large number of potential intervention
61 methods, as well as combinations of these, in the field. Instead, it would be better to start first with those
62 that have the most potential, both in terms of success at reducing the rate of the disease and the costs for
63 implementing the strategy. The question is how to identify these strategies.

64 Here we argue that collaborations between empiricists and mathematical modelers can more efficiently
65 identify solutions to HLB. This is because there is a long history of mathematical models of other vector-
66 borne diseases quickly and reliably identifying the parameters of the host-vector-pathogen system that
67 are most sensitive to perturbations and thus controls. By coupling these models that describe benefits
68 with the economics costs of various interventions, combined cost-benefit models can quickly and reliably
69 guide the formidable task of empirically testing HLB interventions. Indeed, mathematical models can
70 provide insights into the cost effectiveness of lone and combined intervention strategies faster than almost
71 any other approach. They can help efficiently target experiments and field data collection on particular
72 critical factors and interventions, and outcomes then serve as ways to test and validate the models. Thus,
73 by combining appropriate models with laboratory and field experiments, we expect to develop more
74 cost-effective interventions more quickly than using empirical approaches alone.

75 The usefulness of mathematical models

76 Mathematical models for disease systems were first analyzed by Kermack and McKendrick (1927),
77 which paved the way for many future models. In these models, often called *SIR* models, individuals
78 move between different compartments depending on their disease status - often “Susceptible”, “Infected”
79 and “Recovered.” More detailed versions of these models have since evolved to include elements such
80 as demography of the population, age structure, exposure periods, asymptomatic individuals, waning
81 immunity and most important for us, vector-borne transmission, which were initially developed by Ross
82 and MacDonald (Ross, 1911; Macdonald, 1952, 1961). The purpose of these mathematical models falls
83 into two main categories, sometimes referred to as “tactical” or “strategic” models (Nisbet and Gurney,
84 1982). In the latter case, the question the modelers wish to answer is “What could possibly happen?” They
85 aim to find general conclusions that can be used to understand the drivers of population change across

86 many systems. The models are often poor representations of real data. Tactical models are inherently
87 connected to a system and to data collected. Their focus is to make predictions but their answers are only
88 applicable to that one system and are not easily generalized. Furthermore, they usually are unable to show
89 why things occur as they give no information on the drivers of the system. By connecting strategic models
90 more closely to data, it is possible to make qualitative predictions and yet retain understanding of what are
91 the important elements of the system - so that it is possible to understand the effects of targeting specific
92 parameters for control. One of the methods for ensuring that the qualitative predictions are sensible is
93 through sensitivity analysis - analyzing the importance of different parameters on key disease measures.
94 Sensitivity analysis can alert us to cases when we need more data to be sure of our predictions. However,
95 it also highlights which parameters are best to change if we want to affect some aspect of the system, such
96 as when we wish to manage populations or disease outbreaks. Further additions to strategic models, which
97 can make their predictions stronger, are the ability to connect them intimately to cost analysis – and to
98 optimize the solution. That is, to be able to choose, based on some measure of profit, which management
99 strategy out of many is the best. Of course, the measure of profit can change depending on the aim of
100 the study and can be limited by resource use. One power of mathematical models is that they are able to
101 consider any possible number of intervention strategies, compare them cost-effectively, and do so quickly.

102 In addition to the extent and speed at which models can consider intervention strategies, models can
103 also consider spatial and temporal scales that are often not feasible in experiments (Gilligan and van den
104 Bosch, 2008), or theoretical approaches to HLB management that might not have been considered by
105 the citrus industry. Thus models can provide “outside-the-box” tactics to battle this devastating disease.
106 Most experiments cannot logistically test landscape-level disease spread that occurs across multiple years,
107 but this is something that is regularly done with mathematical and statistical models. As an example of
108 “outside-the-box” tactics that models can provide, efforts have been made to control some vector-borne
109 diseases by releasing sterile vectors, which subsequently reduce the vector population and can control
110 or even eliminate the disease (Thomé et al., 2010; Harris et al., 2012). Although this is not presently a
111 reality for HLB, models can test whether this could be an effective control measure for this system and,
112 for instance, provide guidelines on how many sterile psyllids would have to be released to control or
113 eliminate HLB, thus providing insights into the feasibility of this and other hypothetical control strategies.

114 Here, we provide a case for the more thorough integration of data-driven modeling to HLB control.
115 We first provide case studies in other vector-borne crop disease systems where models were critical to
116 identifying cost-effective management strategies, and focus on vector-borne diseases in plants, similar
117 to HLB. Next, we discuss previous mathematical models of HLB to reveal how modeling has already
118 advanced study of the HLB system. We then provide an example of how a mathematical model for malaria
119 can be used to describe HLB transmission and the potential insights it can yield. In particular, how it can
120 identify parameters that require further experimentation or the success of potential intervention strategies.

121 **MATHEMATICAL MODELS OF VECTOR-BORNE PLANT DISEASES**

122 Plant viruses transmitted by arthropod vectors are a major source of yield losses, infecting a wide range
123 of crop plants. However, the biological details – such as the role of alternative hosts of vectors, the rate of
124 migration, and the seasonality of disease – differ immensely between crop systems and sites. This means
125 that our understanding of disease dynamics and control in one system may not apply to other sites or crops.
126 One way to bridge this control gap is to incorporate biological knowledge into mathematical models that
127 predict disease dynamics and how yield loss will respond to interventions. Models can compare, using a
128 common currency, the potential impact of different interventions by examining sensitivity to parameters
129 that represent different strategies. Previous studies have strategically used models to disentangle the
130 potential role of vector migration, spillover from alternative hosts, and control measures (spraying, netting,
131 phytosanitation) across a range of diseases (e.g., Fishman et al. (1983); Kendall et al. (1992); Holt et al.
132 (1997, 1999); Smith et al. (1998); Robert et al. (2000); Zhang et al. (2001); Jeger (2000); Smith and Holt
133 (1997)). For illustration, we highlight a few key examples here.

134 Holt et al. (1997) describe an African cassava mosaic geminivirus (ACMV) outbreak in cassava,
135 transmitted by a cassava-specific whitefly strain, which was then sweeping through Uganda. The virus
136 also spreads through stem cuttings, the main propagation method for cassava in Africa. Potential control
137 options included phytosanitation (use of uninfected cuttings) and roguing (removal of infected plants).
138 Phytosanitation would be more effective if infected cuttings were driving disease spread, whereas roguing
139 would be more important in a largely vector-driven epidemic. The authors addressed the dynamics and

140 control of this disease using a model that tracks susceptible and infected plants and non-infective and
141 infective vectors, using a version of the Lotka-Volterra predator-prey model with density dependence in
142 both plant and vector. Because there are no alternative vectors or hosts, a minimum density of cassava
143 is required to sustain whitefly populations. The model uncovered otherwise cryptic disease dynamics.
144 Namely, disease cycles occurred when transmission was only via vectors, whereas when infected cuttings
145 were used in a frequency-dependent manner (i.e., as a low proportion of the total cuttings), disease
146 incidence had a sharp threshold. In this situation, it was difficult to detect when the system was close to a
147 critical transition from low to high disease incidence, causing a collapse of uninfected plants. As a result,
148 crop intensification could increase disease incidence gradually while imperceptibly pushing the system
149 toward collapse. Roguing does not reduce disease incidence but can prevent collapse by pulling the
150 system away from the critical threshold, providing a hidden benefit that would not be detectable without
151 the model.

152 In a later paper, Holt et al. (1999) describe how tomato yields in India suffered massive losses (47-85%)
153 from a whitefly-vectored tomato leaf curl geminivirus (TLCV). In contrast to the cassava example, tomato
154 was only an occasional host for this whitefly, and spillover from other perennials and weedy plants drove
155 vector and virus dynamics. In this context, the authors asked “what is the best method for disease control?”
156 Because most of the vector lifespan occurs on other hosts, the authors adapted a previous general model
157 framework (Jeger et al. 1998) to decouple vector dynamics from crop dynamics. The parameterized
158 model could match epidemic curves for susceptible and resistant varieties, although it did not reproduce
159 the 100 percent prevalence that can occur in fully susceptible populations. Sensitivity analyses were
160 then used to explore different disease management options. Because the tomato crop was a sink for
161 whiteflies and TLCV, interventions that reduce vector immigration and survival were predicted to be
162 most effective. The authors’ models suggested that the most effective disease control method would be
163 to distribute netting treated with a persistent insecticide and colored yellow on the crop side; the netting
164 would increase vector mortality and decrease vector immigration and, because the flies are attracted
165 to yellow, the yellow coloring on the crop side would increase emigration. However, because vector
166 migration from uncontrolled populations in alternate plant hosts would sustain the supply of migrants,
167 interventions would need to be continuous to be effective in the long term. Thus, although this system –
168 a whitefly-vectored geminivirus – is superficially similar to the previous cassava example, it highlights
169 the importance of rigorously considering vector, virus, and host biology in a model to design effective
170 interventions. The insecticide-treated, yellow-colored netting devised here is an example of the value of
171 combining complementary approaches to disease control described above, which often only become clear
172 after examining model outcomes.

173 MATHEMATICAL MODELS AND HLB

174 Few mathematical models of HLB currently exist that analyze how HLB spreads within individual trees,
175 within a citrus grove, or from grove to grove. We review here those models which have been applied to
176 HLB because they demonstrate the major insights models have already provided to this disease system.
177 Recent modeling of HLB includes Jacobsen et al. (2013), Parry et al. (2014) and Lee et al. (2015).
178 These articles elucidate the spread of HLB using three different approaches, namely through mechanistic
179 modeling, statistical analysis, and individual-based modeling, respectively. All of these approaches have
180 benefits and offer insights on different aspects of the system.

181 Jacobsen et al. (2013) use mechanistic modeling that is an elaboration on an SIR-type compartment
182 model to understand disease dynamics. Mechanistic models such as these are among the simplest
183 approaches because they do not necessarily require direct parameterization from experimental data.
184 Nevertheless, they still can provide important insights. Jacobsen et al. (2013), model the number of
185 trees within a grove that are in four classes: susceptible; infected but not symptomatic; infected and
186 symptomatic; and dead. With their model, Jacobsen et al. (2013) analyze how the numbers in each class
187 change over time due to bacterial transmission between trees and psyllids. The focus is on what is the
188 range of potential outcomes of disease spread, rather than using a directly parameterized model to make
189 quantitative predictions, i.e. it is a strategic model. However, with the speed of implementing mechanistic
190 modeling and the freedom to consider ranges of solutions, it is possible to find general insights quickly.
191 For example, the elegantly basic model of Jacobsen et al. (2013) suggested a rather counter-intuitive
192 outcome: if infected trees leave behind infected root stock when rogued that can infect trees newly planted
193 at that location, the best control strategy is actually not to rogue at all. This is because the soil is acting

194 as a reservoir to continue disease spread. However, this relies on the assumption that dead trees do not
195 spread infection which may be false, at least for a short time. Thus, the mathematical model has led to a
196 set of concrete outcomes linked to explicit assumptions, both of which can guide further experimentation.

197 The work of Parry et al. (2014) builds upon the framework of the mechanistic model by fitting a
198 spatially explicit disease model in which trees are either Susceptible, Exposed, Infectious, Detected or
199 Removed using data from Southern Garden's citrus groves. It is primarily a methods paper, using HLB
200 as a case study. Specifically, this modeling entailed estimating parameters from a newly emerged HLB
201 outbreak, that could then be used to predict future disease spread and the impact of control strategies from
202 the early stages of the epidemic. The methods are much more complex, both in terms of mathematics
203 and computational implementation. The available data are discrete snapshots of the disease status of the
204 whole grove – often the case with HLB-infected groves. Using censored detection data with no means to
205 determine the actual exposure and infection time for each tree necessitates specialized statistical methods
206 and bespoke software. Their method is able to determine the transmission process from tree to tree in
207 the presence of psyllid management practices - previous modeling of this sort required the pure disease
208 system without external interference through control. From their modeling, they also determine the effect
209 of tree age on transmission parameters and show that host susceptibility is seasonal, leading to better
210 estimates of parameters for future use. The ability to gain so much information from little data results in
211 better predictions for the continued epidemic and the capability to control the current and future outbreaks.
212 While experiments can be used to calculate estimates for such parameters as infection times or probability
213 of successful transmission, this is not possible when an infection has just emerged. Thus, this modeling
214 allows us to implement control strategies straightaway without losing our ability to estimate necessary
215 epidemiological parameters to predict the spread of the epidemic.

216 Finally, Lee et al. (2015) combine experiments and individual-based mathematical models. The
217 main experimental result was that, despite being asymptomatic, the host plant can become infectious
218 in a shorter time than previously thought, within 15 days. They used these experimental data in their
219 individual-based model, which describes how the pattern of HLB spread in a grove depends upon the
220 location within the grove that psyllids initially invade. Their model revealed that the average time until a
221 grove is 100% infected is much lower if the psyllids arrive by wind into the center of the grove than if
222 they invade the grove's edge. Thus, if the grower knows that the psyllids were blown in by wind, they
223 should expect that a more intense control strategy is necessary to have any chance of stopping infection.
224 Through mathematical modeling, Lee et al. (2015) also found that it is possible for the whole grove to
225 be infected before the first symptoms appear on any tree. From this, they emphasize the need to control
226 psyllid populations regardless of whether any trees have shown symptoms because transmission may
227 already be occurring from asymptomatic trees. Importantly, both of the latter two modeling approaches
228 involved a close integration of the model with biological data to estimate parameters and validate model
229 results. Model-data integration greatly improves the ability of mathematical models to accurately predict
230 best management practices to combat HLB.

231 Additionally, modeling papers exist in which the focus is controlling other citrus diseases rather than
232 specifically HLB. Cunniffe et al. (2015) is a good example of a modeling paper that aims to provide
233 useful recommendations to stakeholders such as policy makers and growers, with explanations of why
234 those recommendations are best. The authors include publicly-available software to allow stakeholders to
235 interact with the model, to understand how a strategy of roguing within a radius of detected infected trees
236 would be affected by different roguing radii and the stochastic nature of disease spread. Their focus is on
237 citrus canker but they include HLB as a second example, with the result that optimal roguing radii can be
238 found dependent on the level of risk aversion of the grower. Similarly, Cunniffe et al. (2014), using Bahia
239 bark scaling of citrus, illustrate that mathematical models are able to provide useful recommendations for
240 roguing and tree spacing strategies, even when epidemiological knowledge of the disease is limited.

241 **A PARAMETERIZED HLB MODEL THAT CONSIDERS ECONOMIC COSTS** 242 **AND BENEFITS**

243 We provide an example of a mathematical model for HLB to illustrate how even simple models can
244 provide useful information for stakeholders, laboratory and field experiments and development of new
245 intervention strategies. We highlight how sensitivity analysis can inform which parameters are lacking
246 in data, thereby encouraging more experimental studies, or which parameters should be targeted for
247 intervention. We demonstrate how to incorporate interventions and economic costs and benefits into a

248 plant disease model and the types of information that models can give us. To do this, we use a similar
249 mechanistic modeling approach as Jacobsen et al. (2013) whilst incorporating realistic parameter values
250 including data on the temperature dependency of psyllid vital rates.

251 **Model development and assumptions**

252 We adopt a previous model developed by Parham and Michael (2010) for malaria, with some differences
253 in parameter interpretation. Of particular note, the “biting rate” for mosquitoes will instead be the “feeding
254 rate” for psyllids. The model is parameterized using data from the HLB system (see below). The use of a
255 malaria model highlights the broad applicability of mathematical models that can allow understanding of
256 many vector-borne systems by studying one in detail. The main components of the model are similar to
257 traditional models of vector-borne disease developed by Ross & Macdonald (Macdonald, 1952), also for
258 malaria. Citrus trees are categorized as either Susceptible or Infected, and adult psyllids are Susceptible,
259 Exposed, or Infected, where Exposed indicates that the psyllids are infected but are not yet able to pass
260 the disease on to another tree (Figure 1). The development of eggs and nymphs is included within the
261 birth rate of psyllids. A very small rate of natural death of susceptible trees occurs. An adaption of the
262 malaria model is that we include roguing of infected trees. After an incubation period included in our
263 model through a time delay, infected trees can transmit infection (Gottwald, 2010). Realistically, most
264 infected trees are asymptomatic at first but we do not change the model to include an asymptomatic stage
265 as we wish to stay consistent with the malaria model. Instead, we set the average time to rogue trees to be
266 long enough that newly infectious trees are unlikely to be rogued. The sum of trees dying by natural death
267 or roguing equals the total number of trees removed, which are tracked to estimate the costs of roguing.
268 All of these removed trees are assumed to be immediately replaced by susceptible trees in the grove, thus
269 the grove size remains constant. Transmission of infection can occur when an infected psyllid feeds off a
270 susceptible tree, or vice versa. Psyllids have a constant feeding rate which is independent of the number
271 of trees. We assume that the grove has 100% susceptible trees initially, with psyllids feeding freely from
272 the trees. At time 0, we introduce one infected tree. We consider the change in numbers of susceptible,
273 infected and removed trees for the following 20 years to understand the effects of the initial infection
274 on the whole grove. A full description of the model, with parameter values and information on how we
275 include intervention strategies, is given in Article S1.

276 **Baseline Model Parameterization and Exploration**

277 An important aspect of our model compared with previous models of HLB is our attention to the seasonality
278 inherent in the psyllid life history. Psyllids are ectotherms and thus will be sensitive to fluctuations in
279 temperature both daily and throughout the year. The thermal physiology of ectotherms has been explored
280 in depth, and it is widely recognized that most traits exhibit unimodal patterns – i.e., performance is
281 low at cold temperatures, ramps up to an optimum, and then falls off as temperature increases further
282 (Dell et al., 2011; Amarasekare and Savage, 2012). Recent work on malaria indicates that it is important
283 to incorporate the thermal performance of vectors into disease transmission models (Mordecai et al.,
284 2013; Johnson et al., 2015). Based on data from Liu and Tsai (2000) and average monthly temperatures
285 in Florida, we include yearly variation in psyllid vital rates, specifically fecundity, development rate,
286 probability of developing from egg to adult, and death rate (see Article S1 and Figure S1.1).

287 For our other parameters, such as feeding rate, extrinsic incubation period, and probability of successful
288 transmission between tree and psyllid (and vice versa), we obtained data from a variety of sources including
289 Pelz-Stelinski et al. (2010); Lee et al. (2015); Gottwald (2010); Martini et al. (2015). For full details of
290 parameter values and their sources, see Table S1.2.

291 We build in expected costs, income and profits into our model to assess the impact of disease on
292 the grower and the most cost-effective control strategies. We include the cost of removing a tree and
293 replanting with a new disease-free tree, and the cost of our intervention strategy namely the cost of one
294 day of insecticide spraying. These costs, as well as the expected profits from susceptible, infected and
295 treated trees, are estimated from Stansly et al. (2014); Spreen et al. (2006). We assume the profits are
296 constant over time for simplicity (with a discount factor); in reality, profits will change over the course
297 of the outbreak due to changes in supply of citrus (FASS, 2015). Further details of the inclusion of cost
298 estimates in our model can be found in Article S1.

299 We first present the model predictions for spread of HLB within a single grove with only roguing.
300 Studying this base case provides the platform for understanding how effective intervention strategies are
301 at reducing disease prevalence. Next we perform a sensitivity analysis to examine which parameters seem

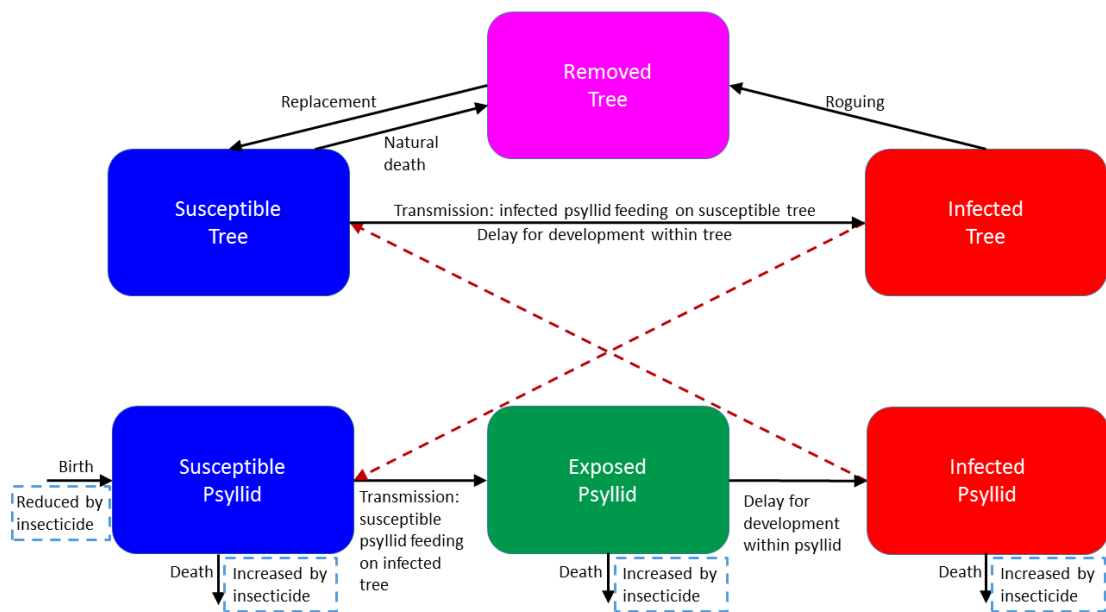


Figure 1. A schematic of the model system showing transitions to different categories for trees and adult psyllids. Trees are either Susceptible, Infected or Removed. Adult psyllids are either Susceptible, Exposed or Infected. Black arrows show the transitions between compartments. Red arrows show the necessary interactions between trees and psyllids to obtain transmission. Light blue dashed boxes highlight how our intervention strategy (see §) impacts transitions within the model.

302 to most impact disease dynamics. We then evaluate the effectiveness of a commonly used control strategy,
 303 insecticide, at counteracting disease prevalence. We assess the cost-effectiveness of this strategy, which
 304 can lead to non-intuitive conclusions about the best strategy to implement.

305 **Results from the base model with only roguing**

306 With no intervention strategy other than roguing, the disease spreads quickly throughout the grove such
 307 that over 90% of the trees are infected within the first 5 years (Figure 2). After 5 years, the constant
 308 replacement of infected trees with new susceptible trees is balanced by new infections, such that the
 309 number of infected trees remains constant across years (with some seasonal variation). After 20 years (see
 310 Figure S2.1), roguing has resulted in replacing 160 trees for a grove size of 101 trees - clearly a costly
 311 control strategy.

312 In both summer and winter the temperature in Florida is not well suited for psyllids, which causes
 313 clear fluctuations in psyllid population abundance twice each year (Figure 2B); the bigger dip occurs each
 314 summer when temperatures are too high for psyllids to produce eggs. However, their high fecundity the
 315 rest of the year allows the psyllid population to bounce back quickly and be effective at spreading disease.
 316 Approximately a third to a half of psyllids are infectious, leading to a large endemic situation in the
 317 trees. However, roguing prevents the grove from becoming 100% infected. A potential strategy to reduce
 318 disease prevalence would be roguing trees more quickly after they become infectious. We investigate how
 319 changing the average time until a tree is rogued affects both the maximum prevalence and the number of
 320 removed trees after 20 years (Figure S2.2). Roguing trees sooner reduces the peak number of infected
 321 trees, but this is outweighed by the significant increase in number of trees that need replaced. However,
 322 roguing can have benefits when implemented alongside other control strategies which target different
 323 aspects of the disease spread, such as the role of the vector.

324 **Sensitivity Analysis**

325 Through sensitivity analysis, we can assess which parameters are influential in the spread of disease within
 326 a grove, highlighting which parameters are important to target for intervention or for more experimental
 327 study. To do this, we focus on R_0 , the expected number of secondary cases, i.e. the number of trees
 328 which will become infected due to a single infected tree present within a grove (see Article S1). R_0 is

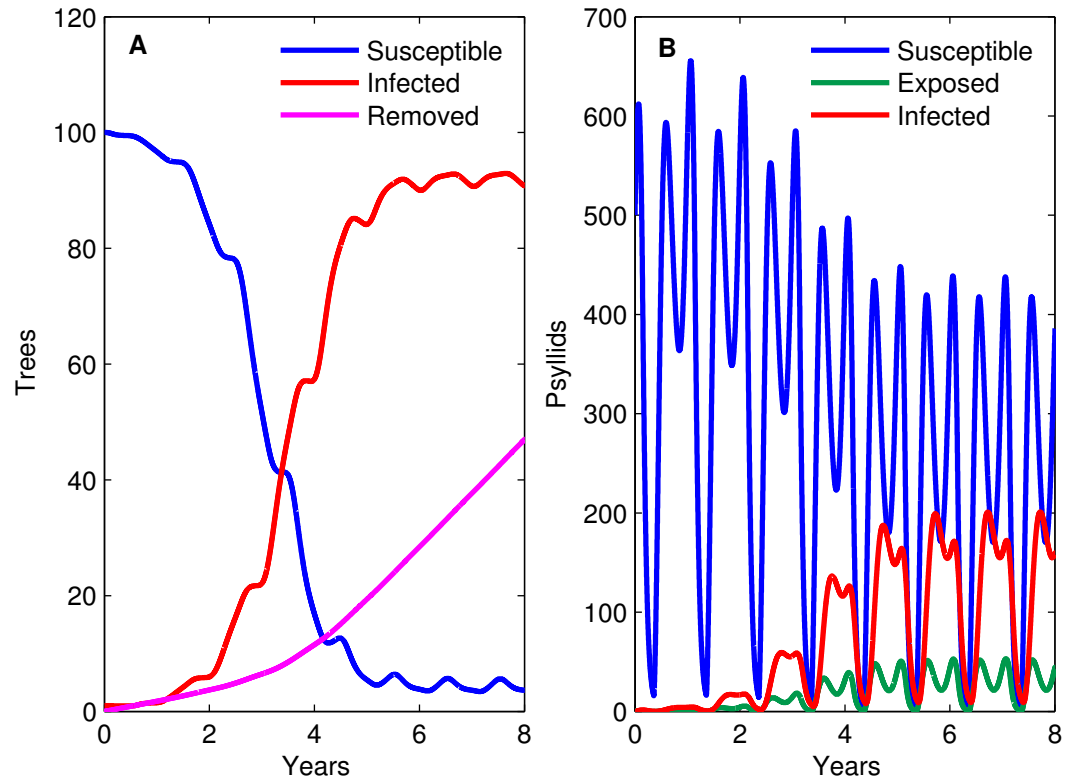


Figure 2. The changes in numbers of susceptible and infected trees and psyllids over 8 years when one tree is infected at time 0. In A, alive trees are either Susceptible (blue) or Infected (red), and Removed trees are also plotted (purple). In B, psyllids are Susceptible (blue), Exposed (green) or Infected (red).

329 a combination of parameters related to both the psyllids and the trees, but with a higher proportion of
 330 the former. We perform two different types of sensitivity analysis because we have both temperature
 331 dependent parameters and constant parameters.

332 As outlined earlier, we have data on how some psyllid vital rates are dependent on temperature; in
 333 Article S1, Figure S1.1, we fit response curves to those data. These response curves describe how four
 334 parameters are affected by temperature: fecundity of female psyllids (EFD); the probability of egg to
 335 adult survival of psyllids (p_{EA}); psyllid development rate (MDR); and psyllid death rate (μ). Performing
 336 sensitivity analysis with these parameters, we can assess how changes in temperature propagate through
 337 the different parameters to affect R_0 (Figure 3A).

338 The fecundity of female psyllids (EFD) has a significant impact on R_0 at low and high temperatures
 339 (Figure 3A). Experimental studies demonstrate that psyllid fecundity is greatly reduced for low and high
 340 temperatures. Since R_0 is very sensitive to this result, it highlights the need to perform more experimental
 341 studies of psyllid fecundity for a wide temperature range to ensure its validity. Figure 3A indicates
 342 that μ is influential in reducing R_0 at mid to high temperatures, whereas it is not influential at low
 343 temperatures. Therefore, an intervention strategy targeting psyllid death rate would be most successful if
 344 it is implemented during the warmer seasons.

345 We also perform sensitivity analysis of the constant parameters that are included in R_0 (Figure 3B).
 346 For the following parameters we vary its value by 10% and plot the effect on R_0 : the feeding rate of the
 347 psyllid (a); the probability of successful transmission from psyllid to tree (b); the probability of successful
 348 transmission from tree to psyllid (c); the roguing rate of infected trees (r_1); and the rate of extrinsic
 349 incubation within the psyllid (ϕ).

350 The feeding rate of psyllids (parameter a , Figure 3B) has clearly the most effect on R_0 of all the
 351 constant parameters. This occurs because the parameter is involved in both directions of transmission:
 352 from tree to psyllid and vice versa. However, it is hard to experimentally determine the feeding rate of

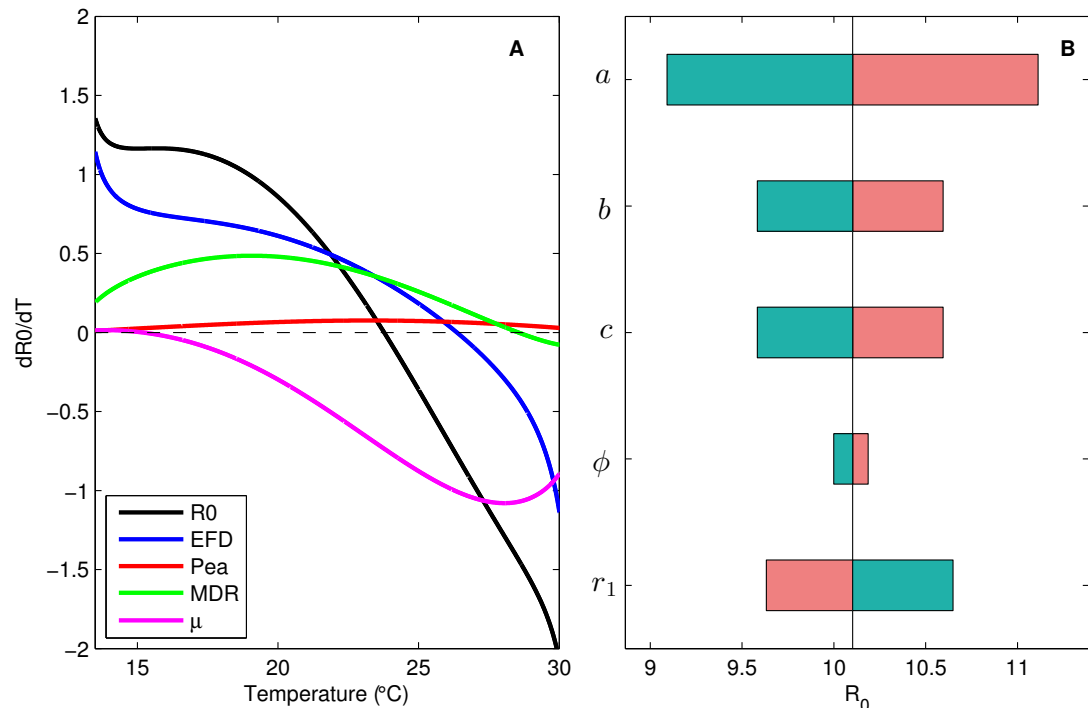


Figure 3. The sensitivity of R_0 to changes in temperature-varying and constant parameters. In A, the change in R_0 , $\frac{dR_0}{dT}$, is plotted against temperature alongside how each of the psyllid parameters contributes to this change in R_0 , denoted by color. The further the curve is from zero, the more contribution that parameter has to changes in R_0 . In B, the sensitivity of R_0 to changes in constant parameters at $T = 23.43^{\circ}\text{C}$, when R_0 is at its maximum ($R_0 = 10.1$). Each parameter is varied by 10% to assess the impact on R_0 at this maximum temperature. Decreasing each parameter by 10% (e.g. $0.9a$) is indicated in green; increasing each parameter by 10% (e.g. $1.1a$) is indicated in pink.

353 psyllids on trees as they do not follow the pattern of one feed per oviposition, such as mosquitoes, and the
 354 nymphs remain attached to tree flush for the duration of this life stage. Thus, it highlights the need to
 355 focus future work on pinning down this parameter more precisely since it is so influential on R_0 , as well as
 356 improving the model to account for psyllid biology. Note that parameter r_1 has the opposite effect to the
 357 other parameters – an increase in r_1 decreases R_0 , whereas the other parameters are positively correlated
 358 with R_0 . The width of the effect on R_0 is slightly larger for r_1 than the other parameters apart from a . We
 359 discuss varying this roguing rate in Figure S2.2 with the result that roguing does reduce disease prevalence
 360 but at the cost of removing many more trees.

361 Insecticide Intervention

362 Based on the sensitivity analysis, in which psyllid death rate has a significant effect on R_0 , and since
 363 insecticide is currently the main control strategy in use, we analyze what is the most cost-effective strategy
 364 to implement insecticide intervention. Whilst many groves are being sprayed with insecticides to control
 365 psyllids and thus HLB (Grafton-Cardwell et al., 2013), the range of methods for insecticide application
 366 across the US is large with differences in number of applications per year and the efficiency of the
 367 insecticide (Qureshi et al., 2014; Rogers, 2008). Thus, there are not obvious scenarios that can be used as
 368 comparisons to test which is the best method. Instead, we assess the insecticide application through a
 369 process more akin to global sensitivity – we vary the level of insecticide efficiency and the number of
 370 days spraying throughout the year over a wide range to capture the current state of play of insecticide
 371 application. Our intention here is to present preliminary results and proof-of-concept for the use of a
 372 vector-driven epidemiological model to compare the effectiveness of different control scenarios in an
 373 isolated grove.

374 When insecticide is applied to the groves it targets all adult psyllids through increasing their death rate.

375 It also reduces the birth rate of psyllids, to represent the insecticide killing eggs and nymphs (Figure 1).
376 We apply insecticide spray in both spring and autumn. Therefore, insecticide spraying occurs at mid-range
377 temperatures, which Figure 3A indicated was the best time to target the psyllid death rate. Both spring and
378 autumn sprays will involve spraying for the same number of consecutive days. But between simulations
379 we vary the total number of days spraying each year. For example, a simulation with 20 days spraying per
380 year will have 10 consecutive days at the start of spring and 10 consecutive days at the start of autumn,
381 whereas a simulation with 10 days spraying per year will have 5 days each in spring and autumn. Each
382 additional day of spraying costs more money to the grower. We also varied the effectiveness of the spray
383 and assumed that it correlated positively with its cost; sprays that are not very effective cost approximately
384 \$15 per day to spray, while highly effective sprays can cost up to \$70 per day, for the whole grove. An
385 estimate of \$30 per spray is estimated from Stansly et al. (2014). To see full details on how insecticide is
386 included into the mathematical model and how costs of spraying are calculated, please see Article S1.

387 The number of insecticide application days varies between 10 and 60 days per year split equally
388 between the two spraying sessions, and the efficacy of insecticide applications varies between 60 and 99%.
389 Multiple sprays in a year occur in most groves, with varying ranges of up to 7 sprays (Stansly et al., 2014),
390 monthly (Rogers, 2008), or up to 20 sprays per year (Spreen et al., 2006), using a variety of approved
391 sprays that differ in effectiveness (Rogers, 2008); some sprays can have an average efficiency as low as
392 53% (Qureshi et al., 2014). 60 days is unrealistic logistically in terms of potential insecticide strategies.
393 But it allows us to investigate the effect of very aggressive control. We quantify how the variation in
394 number of days spraying and effectiveness of spray affect the peak number of infected trees and the
395 expected profits from the grove over a 20 year time span (Figure 4).

396 There is a clear pattern that increasing the number of application days leads to a reduction in infected
397 trees and hence reduced disease spread (Figure 4A). However, this is not the case for increasing the
398 effectiveness of the insecticide spray. It does lead to reductions in the peak numbers of infected trees (the
399 change in color occurs sooner for highly effective sprays) but the change is slight. Overall, by increasing
400 the effectiveness of the spray and by spraying for more days, the peak number of infected trees is lessened
401 from 90 to 81 trees. This is not a great improvement but it is lower than was achieved by roguing at a very
402 high rate (Figure S2.2).

403 The increasing costs associated with, and the lack of improvement attained through, using more
404 effective sprays, combine to lead to smaller profits as effectiveness increases (Figure 4B). The additional
405 costs of more effective sprays are not outweighed by the slight reduction in infected trees. In fact, the
406 most cost-effective spraying strategy is 60 days at 60% effectiveness. For a wide range of number of
407 spraying days, more profits are gained through choosing the 60% effective spray than a more effective
408 spray.

409 Figure 4A, B highlights that the best strategy is not to search for a more effective spray but to
410 implement the most aggressive control strategy which is logistically possible. With 60% effectiveness,
411 increasing the number of days spraying always led to significant increases in profits. Therefore the
412 limiting factor of extending the number of spraying days is not diminishing returns, but the ability to
413 perform the insecticide application.

414 For comparison, we consider spraying in summer and winter (Figure 4C, D), rather than spring and
415 autumn which was suggested as the best time from the sensitivity analysis. It is instantly clear that
416 spraying in summer and winter is nowhere near as successful as spraying in spring and autumn. In Figure
417 4C, the reduction in peak number of infected trees is approximately 91 trees down to 90 trees. Thus,
418 the best intervention when spraying in summer and winter is worse than the worst intervention when
419 spraying in spring and autumn, in terms of number of infected trees. This propagates into profits as well,
420 with much lower profits achieved for spraying in summer and winter. This highlights the importance
421 of considering the seasonality inherent in the system, as it will affect when to implement intervention
422 strategies. In Figure 4D, increasing the number of days spraying reduces profits, a reversal of the pattern
423 seen in B. This occurs because increasing spraying days only reduces infection prevalence very little, and
424 therefore there is no significant increase in income to outweigh the extra costs of spraying. Thus, our
425 results validate our sensitivity analysis which indicated that the death rate had most effect on the spread of
426 the disease in mid-range temperatures.

427 We present the results for the expected citrus profits when there is HLB and 1) no intervention, 2)
428 insecticide application, and the ideal but currently unrealistic scenario of 3) no HLB (Table 1). Costs are
429 included in the model as outlined in Article S1. We focus on the most successful intervention strategy

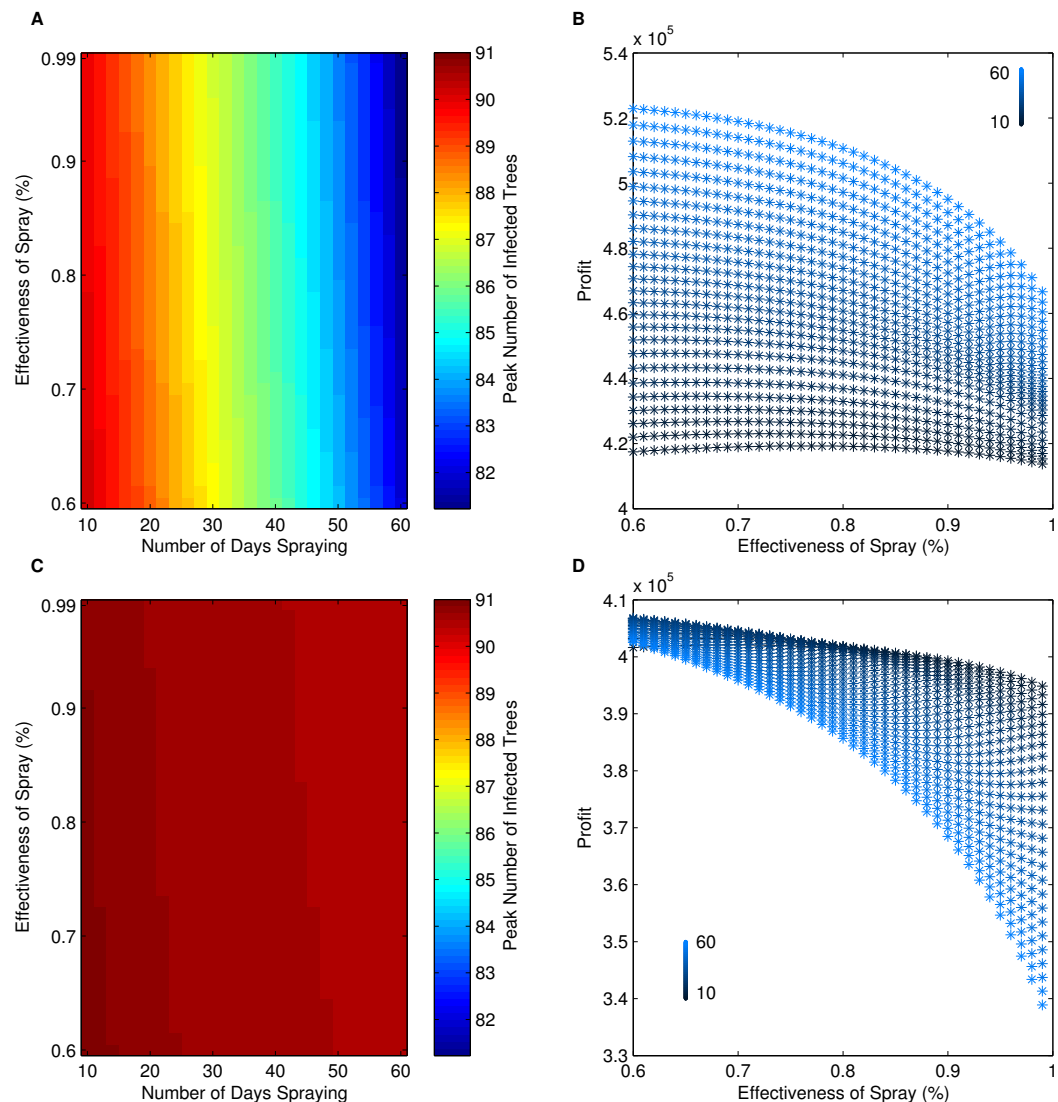


Figure 4. The effect of different insecticide strategies after a 20 year time span. Insecticide targets both the death rate and birth rate of psyllids. In A and B, we spray the insecticide in spring and autumn. In C and D, we spray the insecticide in summer and winter. In A and C, the peak number of infected trees is shown as a function of both the number of days spraying during each year and the effectiveness of the spray, using the same color scale. In B and D, the end profit after 20 years is plotted against effectiveness of spray when a more effective spray correlates positively with cost. As the points change from black to blue, the number of days spraying per year increases from 10 to 60 days as indicated by the key. The number of days spraying is the total per year, split equally between the two spraying regimes.

430 presented, which was spraying for 60 days in spring and autumn, with 60% effectiveness.

431 The large cost of insecticide application is outweighed by the significant increase in income compared
 432 with the no intervention case (Table 1), even if it is not able to match the no disease case. Thus, insecticide
 433 application looks promising. By viewing the profits over a 20 year time frame (Figure 5), it is possible to
 434 gain more understanding of how insecticide profits compare with the other scenarios. All the scenarios
 435 result in similar profits for the first 4 years, until the infected trees have increased to significant numbers.
 436 For the first 9 years, the insecticide strategy manages to keep profits high, nearly matching the no disease
 437 case. This is encouraging, as without intervention most of the grove is infectious after 4 years (Figure 2).
 438 However, the effectiveness of insecticide as an intervention declines the longer it is used. The margin

	No Disease	No Intervention (Fig. 2)	Insecticide (Fig. 4B)
Cost of Removing Trees	\$1155	\$5431	\$3524
Cost of Intervention	-	-	\$8822
Income from Trees	\$768,241	\$374,686	\$544,043
Total Profit	\$766,086	\$369,254	\$531,697

Table 1. The expected costs and income for different intervention scenarios, rounded to the nearest dollar. The insecticide treatment is 60% effective, with 60 days of spraying (Figure 4B). The no intervention strategy includes roguing of infected trees, as in Figure 2. The no disease case includes natural death and replacement of susceptible trees. All other parameters are as in Tables S1.2 and S1.3.

439 between profits from the no disease case and insecticide is ever widening whereas between insecticide
440 and no intervention it stays constant towards the end of the 20 year simulation.

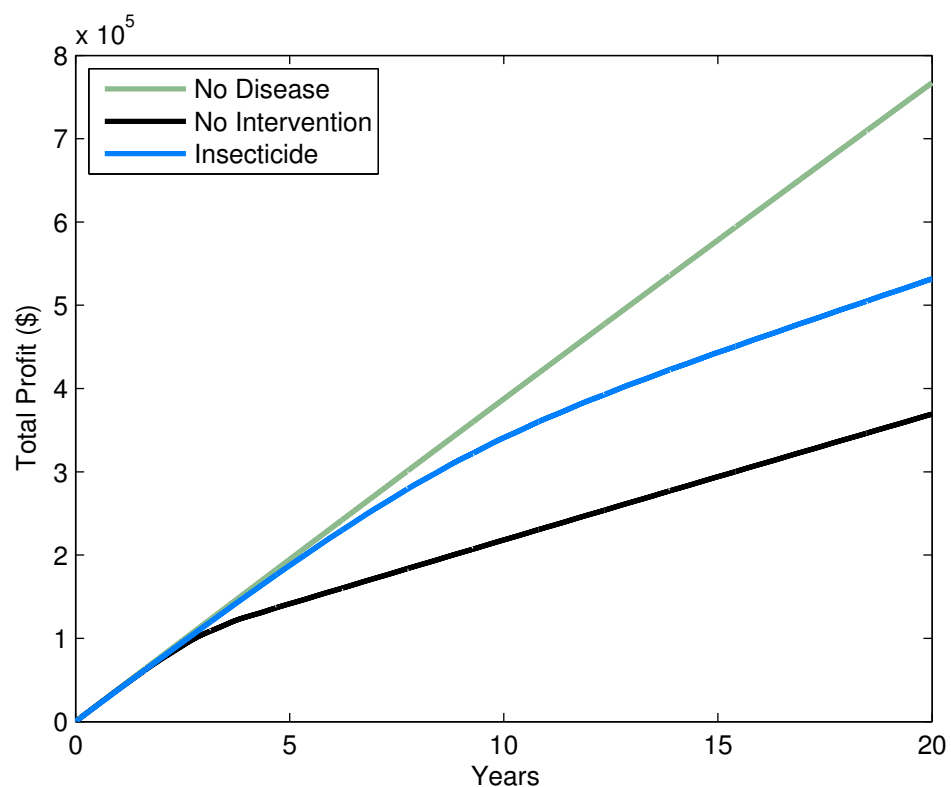


Figure 5. The profit attained by growers over 20 years for different disease and intervention scenarios: the no disease case (green), the no intervention case (black), and insecticide spraying (blue). The insecticide treatment is 60% effective, with 60 days of spraying (Figure 4B). All other parameters are in Tables S1.2 and S1.3.

441 Model Summary

442 We have used a previously existing malaria model and adapted it to Huanglongbing by adding in
443 temperature-dependent parameters for psyllid vital rates, roguing of trees and economic costs. This model
444 is clearly preliminary and only a first step towards understanding the spread of HLB within a grove,
445 with a more HLB-specific model required to be able to capture the full dynamics of the citrus, psyllid
446 and pathogen interactions. However, the relatively simple model presented here, that captures the main
447 features of HLB spread, is able to establish useful recommendations for managing HLB.

448 Using sensitivity analysis, we are able to suggest what new data need to be collected, or which
449 parameters to focus on for potential intervention strategies. In particular, our preliminary analyses suggest
450 fecundity of psyllids should be measured over a finer temperature range to better pin down the temperature
451 window for psyllid egg production, since transmission of infection is strongly affected by when psyllids
452 can produce eggs. Similarly, we suggest the feeding rate of psyllids requires further experimental work
453 because it is an important parameter but the amount of data collected for it so far is small. It could also
454 be dependent on temperature which has not been considered in experimental studies. Often the feeding
455 rate is only inferred from studies assessing success or failure of transmission of HLB between tree and
456 psyllid. But this parameter should be independent of whether transmission occurs. Furthermore, through
457 sensitivity analysis, we propose that the death rate of psyllids, especially during mid to high temperatures,
458 is influential on the spread of the disease and should be targeted for intervention. Performing similar
459 analyses with an HLB-specific model and more data to parameterise it will allow us to shortlist the
460 intervention strategies we examine, at least in the initial stages.

461 Targeting the psyllid death rate through the use of insecticide spray led to a reduction in the disease
462 spread within a grove and increased profits compared with no intervention. One important aspect found
463 was the need to include psyllid temperature dependency and seasonal temperature. This plays a prominent
464 role in the success of intervention strategies, with some times of year much better for reducing infection.
465 However, the degree to which disease is reduced is low even in the best simulations we found. Disease
466 spreads rapidly throughout the grove and the interventions are only capable of maintaining profits rather
467 than eradicating HLB.

468 As stated above, a more HLB-specific model that captures additional factors involved in HLB spread
469 would produce more reliable and more concrete results for implementing management practices for HLB.
470 To achieve this, the most important update to the model would be to consider the adult and nymphal
471 stages of the psyllids separately. In our model, it is assumed that only adult psyllids are able to be infected
472 and are infectious to trees. In reality, the nymphal stage of psyllids has a significant role to play in the
473 transmission of HLB. Experiments have concluded that most psyllids become infected with HLB when
474 they are nymphs and then remain infected for their entire lifespan (Pelz-Stelinski et al., 2010; Hung
475 et al., 2004). Psyllids that become infectious as adults often transmit the pathogen to trees at a lower rate
476 than adults who became infected as nymphs (Pelz-Stelinski et al., 2010; Inoue et al., 2009). However,
477 nymphs usually remain attached to one tree flush in the early nymphal stages and thus do not transmit the
478 disease to other trees (Hall et al., 2013). There is also a slim chance of vertical (transovarial) transmission
479 (Pelz-Stelinski et al., 2010). Therefore, an improvement would be to model the egg and nymph life-stages
480 directly and incorporate the details of how transmission of HLB from psyllid to tree is affected by the
481 psyllid life history.

482 CONCLUSION

483 Collaborations between empiricists and mathematical modelers have the potential to identify solutions to
484 HLB more efficiently and reliably. By incorporating the wealth of knowledge provided by empiricists in
485 other plant disease systems, models have been proven to disentangle the potential drivers of the disease,
486 inform which aspects of the system to target to control disease and the potential efficiency of those
487 intervention strategies. This success can also transpire for HLB, allowing profits to be maintained and the
488 possibility of disease eradication. We have shown that even simple models for HLB can provide useful
489 recommendations for moving forward with disease management. By collaborating more closely with
490 empiricists, these recommendations will improve in scope, reliability and accuracy. Models can highlight
491 our lack of understanding in crucial areas, directing future lab and field work. For example, our model
492 demonstrated that the feeding rate of psyllids is an important component of disease spread, but it can be
493 difficult to find experimental data on this parameter measured the way a modeler would wish – how many
494 feeds per time per vector stage per temperature. Therefore, better communication between modelers and
495 empiricists is required, benefiting both groups through improved data collection and models.

496 We highlight here the tools that mathematical models can bring to the table for fighting HLB. For
497 simpler models, the strength lies in the sensitivity analysis, which allows models to be improved by
498 suggesting better data collection. For future models, perhaps most useful of all is the ability to test
499 different interventions and combinations of strategies in a short time frame to predict which will be
500 the most successful. Improvements can be made to our model to include more aspects of psyllid and
501 tree biology and different intervention strategies can be considered relatively quickly. Other adaptations

502 could be introduced to consider multiple groves, as well as introducing uncertainties in the host response,
503 pathogen and vector dynamics. This reduces the amount of time required performing field experiments to
504 determine if the interventions could work. Furthermore, the ability for economic considerations to be
505 integrated into mathematical models to allow for optimal management of the intervention is a strength
506 that can not be rivaled by other methods. Decisions for future management and control can be made based
507 upon informed analysis of the costs and benefits involved rather than intuition. Therefore, we believe that
508 mathematical models are a powerful method that need to be utilized further for managing the spread of
509 Huanglongbing.

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