Industrial bees: the impact of apicultural intensification on local disease prevalence.

Lewis J. Bartlett[1,5*], Carly Rozins[1,2*], Berry J. Brosi[3], Keith S. Delaplane[4], Jacobus C. de Roode[5], Andrew White[6], Lena Wilfert[1,7], Michael Boots[1,2,†]

1 Centre for Ecology and Conservation, University of Exeter, TR10 9FE, UK

2 Department of Integrative Biology, University of California, Berkeley, CA, 94720, USA

3 Department of Environmental Sciences, Emory University, Atlanta, GA, 30322, USA

4 Department of Entomology, University of Georgia, Athens, GA, 30602, USA

5 Department of Biology, Emory University, Atlanta, GA, 30322, USA

6 Department of Mathematics, Heriot-Watt University, Edinburgh EH14 4AS, UK

7 Institute of Evolutionary Ecology and Conservation Genomics, University of Ulm, 89069 Ulm, Germany

* These authors contributed equally to this work.

† mboots@berkeley.edu

Abstract

1) It is generally thought that the intensification of farming will result in higher disease prevalences, although there is little specific modelling testing this idea. Focussing on honeybees, we build multi-colony models to inform how 'apicultural intensification' is predicted to impact honeybee pathogen epidemiology at the apiary scale.

2) We used both agent-based and analytical models to show that three linked aspects of apicultural intensification (increased population sizes, changes in population network structure, and increased between-colony transmission) are unlikely to greatly increase disease prevalence in apiaries. Principally this is because even low-intensity apiculture exhibits high disease prevalence.

3) The greatest impacts of apicultural intensification are found for diseases with relatively low R_0 (basic reproduction number), however, such diseases cause little overall disease prevalence and therefore the impacts of intensification are minor. Furthermore, the smallest impacts of intensification are for diseases with high R_0 values, which we argue are typical of important honeybee diseases.

4) *Policy Implications:* Our findings contradict the idea that apicultural intensification by crowding honeybee colonies in large, dense apiaries leads to notably higher disease prevalences for established honeybee pathogens. More broadly, our work demonstrates the need for informative models of all agricultural systems and management practices in order to understand the implications of management changes on diseases.

Key Words: apiculture, beekeeping, agriculture, intensification, infectious disease, mathematical model, agriculture, disease prevalence

Introduction

Infectious diseases have significant impacts on agricultural sustainability (Brijnath, Butler, & McMichael, 2014) and profitability (James, 1981). A key question is how agricultural intensification and novel agricultural practices impact the emergence and epidemiology of infectious disease (Cressler, McLeod, Rozins, Hoogen, & Day, 2016; Gandon, Hochberg, Holt, & Day, 2013). It is generally assumed that intensification increases vulnerability to severe disease outbreaks (Jones et al., 2013; Kennedy et al., 2016; Mennerat, Nilsen, Ebert, & Skorping, 2010), but there is relatively little empirical data and therefore epidemiological theory is needed to address this problem (Atkins et al., 2013; Rozins & Day, 2016). Here we build specific models of apiary-level intensification in commercially farmed honeybees to examine the impact of industrial-scale management practices on honeybee infectious disease prevalence.

Honeybee health and the apicultural industry are under threat from a variety of pressures (Ghazoul, 2005; vanEngelsdorp & Meixner, 2010), including parasites and pathogens (Budge et al., 2015; De la Rúa, Jaffé, Dall'Olio, Muñoz, & Serrano, 2009; Potts et al., 2010). There is a growing body of literature documenting the damage that emerging or re-emerging diseases (Wilfert et al., 2016) are causing in apiculture (Jacques et al., 2017; Kielmanowicz et al., 2015) and native pollinators (Cohen, Quistberg, Philpott, & DeGrandi-Hoffman, 2017; Fürst, McMahon, Osborne, Paxton, & Brown, 2014; Graystock, Blane, McFrederick, Goulson, & Hughes, 2016; Manley, Boots, & Wilfert, 2015; McMahon et al., 2015; McMahon, Wilfert, Paxton, & Brown, 2018). Evidence exists supporting a link between the risk of these diseases and specific apicultural practices (Giacobino et al., 2014; Mõtus, Raie, Orro, Chauzat, & Viltrop, 2016; Pacini et al., 2016). However, the evidence is geographically limited, lacking in mechanistic underpinning, or contradictory even within this small collection of studies. For example, Mõtus et al. (2016) report that larger apiaries show marginally higher incidence of ectoparasitic *Varroa* mites in Estonia, whilst Giacobino et al. (2014) did not find this association in a similar study in Argentina. It is therefore critical that we learn how different apicultural practices impact disease outcomes (Brosi, Delaplane, Boots, & de Roode, 2017). The need for an epidemiological framing of honeybee diseases has been frequently discussed (Brosi et al., 2017; Fries &

Camazine, 2001) in both empirical (van Engelsdorp et al., 2013) and modelling (Becher, Osborne, Thorbek, Kennedy, & Grimm, 2013) studies, but we lack a modelling framework for disease ecology in honeybees at a scale larger than a single colony.

Honeybees are typically managed in apiaries, which are associated colonies placed together for beekeeping convenience at a single site. Pathogen dynamics at the apiary level are determined both by pathogen transmission within and between colonies. Intensification of apiculture changes apiary ecology in a number of ways, all potentially relevant to disease (Brosi et al., 2017). In particular, increasing the number of colonies and changing the arrangement of those colonies influences epidemiology through changes in both the size and network structure of the population. They both may also increase the rate at which transmission between colonies occurs via more frequent 'drifting' of honeybees (Free, 1958; Neumann, Radloff, Pirk, & Hepburn, 2003). Drift is a key mechanism of between-colony pathogen transmission (Goodwin, Perry, & Houten, 1994; Roetschi, Berthoud, Kuhn, & Imdorf, 2008) and has been invoked as an explanatory mechanism accounting for higher parasite prevalences in larger apiaries (Mõtus et al., 2016).

The intensification of agricultural systems generally means larger, denser population sizes and greater pathogen transmissibility at local (within a population, such as a farm) and landscape (between populations, such as neighbouring farms) scales. To understand these effects in honeybees we build multi-colony models to examine how apicultural intensification is predicted to impact honeybee pathogen epidemiology. We examine the epidemiological consequences of increasing the number of colonies within an apiary, changing colony configurations, and increasing between-colony pathogen transmission.

Materials and Methods

We combine mathematical models and agent-based model (ABM) simulations to make predictions on how intensification affects disease risk, spread, and endemic prevalence within an apiary. The key to our approach is that we capture pathogen transmission both within and between colonies.

We generalise colony arrangements to three unique configurations drawn from experience, classic apicultural literature (Jay 1966) and current experimental work (Dynes, Berry, Delaplane, Brosi, & de Roode, 2019): array, circular and lattice (Fig. 1). We restrict between-colony pathogen transmission to nearest neighbours (see discussion), those in closest proximity to each other (connected by an arrow in Fig. 2). Between-colony transmission is always assumed to be at a lower rate than within colony transmission. The mathematical model allows us to obtain tractable analytical results while the ABM simulations allow us to model disease at the level of the individual bee and consider stochastic effects.

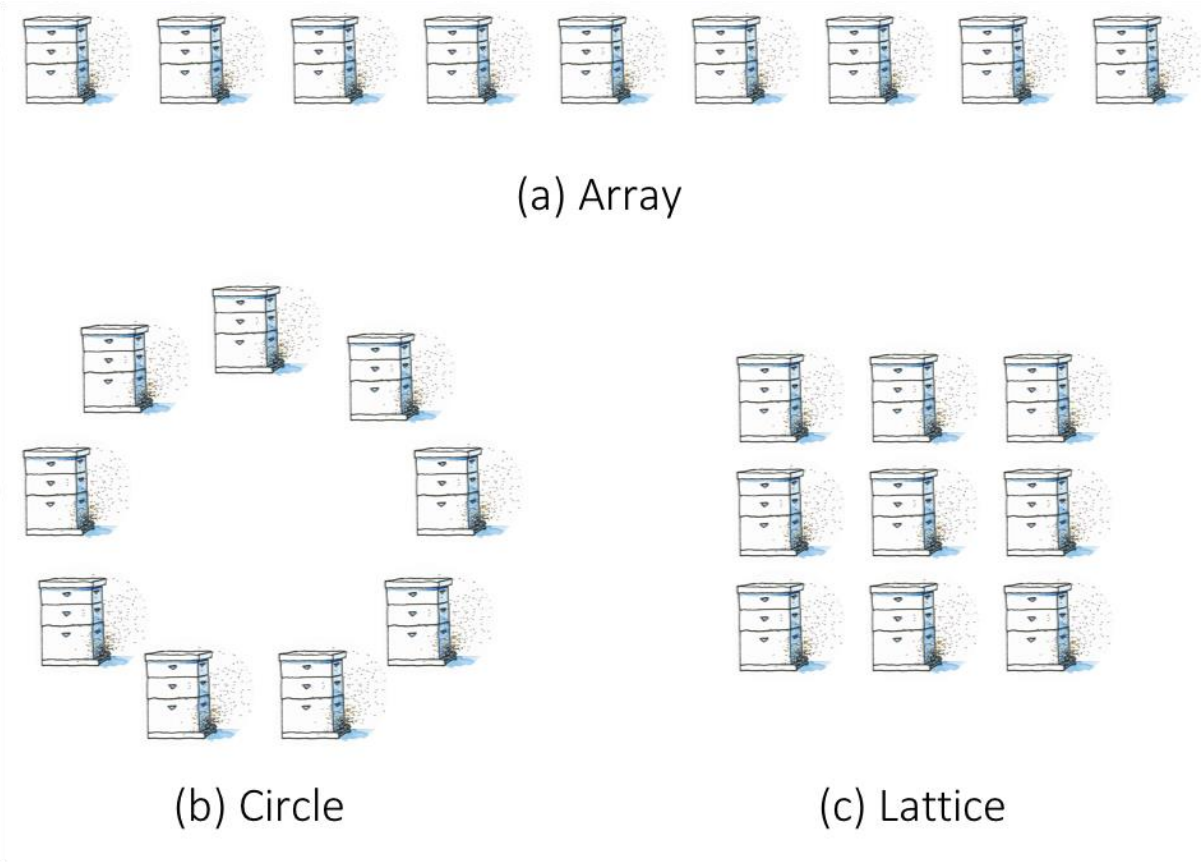


Figure 1. Colony configurations, demonstrated for apiaries with nine colonies.

We first derive a compartmental SI (Susceptible, Infected) model for pathogen transmission within an apiary. The model treats each colony as an individual population and allows for within colony as well as between-colony transmission (for nearest neighbours). Within a colony, honeybees are either susceptible to infection or infected (and infectious). We denote the number of susceptible honeybees in colony *i* at time *t* as $S_i(t)$. Likewise, we denote the number of honeybees in colony *i* infected with the pathogen at time *t* as $I_i(t)$. Susceptible honeybees in colony *i* become infected at rate β_{ij} following contact with an infected bee that resides in colony *j*. We assume that honeybees do not recover from infection. Honeybees are born at rate ϕ, have a natural mortality rate of *m*, and an additional mortality rate of *v* if infected. The following *2n* differential equations, [1], model disease transmission within and between *n* colonies in an apiary.

$$\frac{dS_i}{dt} = -\sum_{j=1}^{n} \beta_{ij} S_i I_j - mS_i + \phi$$

$$\frac{dI_i}{dt} = \sum_{j=1}^{n} \beta_{ij} S_i I_j - (m+v) I_i \qquad [1]$$

The matrix $\beta=[\beta_{ij}]$ will depend on the colony arrangement (see Fig. 1; and S.I. Section 1). The transmission rate between a susceptible and infected honeybee within the colony is *a*, and transmission between neighbouring colonies is *b*. For example, for a 9-colony apiary, the transmission matrices for an array, circular and lattice configured apiary (respectively) are as follows:

$$\begin{bmatrix} a & b & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ b & a & b & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b & a & b & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & b & a & b & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b & a & b & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & b & a & b & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & b & a & b & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & b & a & b \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & b & a \end{bmatrix}, \begin{bmatrix} a & b & 0 & 0 & 0 & 0 & 0 & 0 & b \\ b & a & b & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b & a & b & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & b & a & b & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b & a & b & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & b & a & b & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & b & a & b & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & b & a & b \\ b & 0 & 0 & 0 & 0 & 0 & 0 & b & a \end{bmatrix}, \begin{bmatrix} a & b & 0 & b & 0 & 0 & 0 & 0 & 0 \\ b & a & b & 0 & b & 0 & 0 & 0 & 0 \\ 0 & b & a & 0 & 0 & b & 0 & 0 & 0 \\ b & 0 & 0 & a & b & 0 & b & 0 & 0 \\ 0 & b & 0 & b & a & b & 0 & b & 0 \\ 0 & 0 & b & 0 & b & a & 0 & 0 & b \\ 0 & 0 & 0 & b & 0 & 0 & a & b & 0 \\ 0 & 0 & 0 & 0 & b & 0 & b & a & b \\ 0 & 0 & 0 & 0 & 0 & b & 0 & b & a \end{bmatrix}$$

The corresponding network structures for the above transmission matrices can be seen in Fig. S1. We assume that honeybees are much more likely to become infected by a honeybee that resides within its home colony than by a honeybee from a neighbouring colony (i.e. $a>>b$). Note that for each apiary configuration to be possible and unique, the number of colonies (n) must be a perfect square, $n=L^2$ where $L\geq3$ (see Fig. 1). Therefore, the minimum number of colonies per apiary is 9, which has been observed to be the mean size of a hobbyist or small beekeeping operation (Mõtus et al., 2016; Pocol, Marghitas, & Popa, 2012).

We complement our mathematical model [1] with the ABM; our ABM simulates pathogen spread, through individual bee movements, across an apiary. Apiaries are differentiated by the same characteristics as in the mathematical model; a description of the ABM is available in the S.I. (Section 2) and the model is publicly available (see S.I.). We use the ABM to simulate disease dynamics for both different pathogen phenotypes (varying both pathogen virulence and transmissibility) and different apiary ecologies (varied as previously described in the number of colonies per apiary, layout, and likelihood of bees moving between colonies) (S.I. Figs. S3 & S4); we compare the ABM to the analytical model and use it to test assumptions made elsewhere in the study (Fig. 4a, S.I. Fig. S6).

We can understand the dynamics presented by our models by focussing on the basic reproduction number, R_0. R_0 is a fundamental concept in infectious disease ecology, defined as the average number of secondary infections caused by one infectious individual in an otherwise entirely susceptible population (Anderson & May, 1992). We derive R_0 expressions, using model [1], for each of the apiary configurations. R_0 derivations using model [1] allow us to characterise the relationship between R_0 and pathogen prevalence, defined as the proportion of honeybees within an apiary that are infected at the endemic equilibrium. The R_0 expressions for apiaries with $n>1$ colonies were calculated using the next generation method (van den Driessche & Watmough, 2002), (see S.I. Section 1).

$$R0_{Array} = \frac{\phi}{m(m+v)}\left(a - 2b\cos\frac{n\pi}{n+1}\right) \qquad [2a]$$

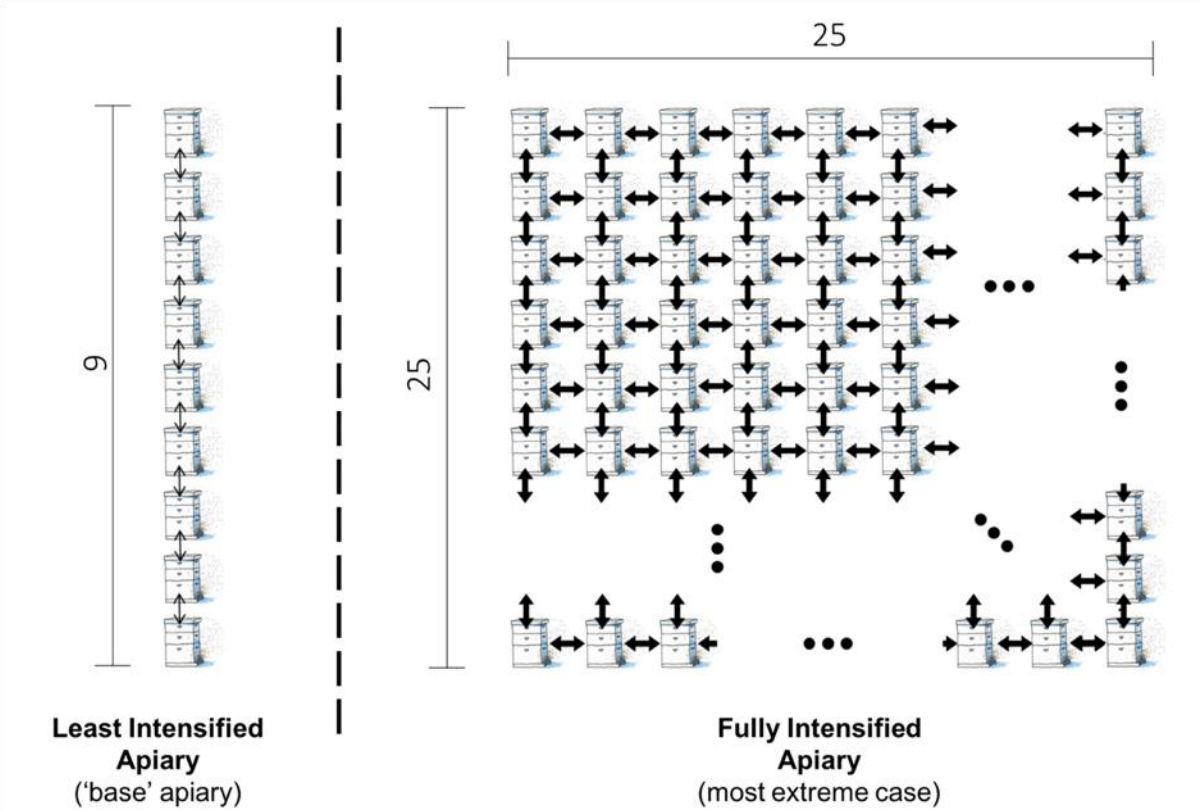
$$R0_{Circle} = \frac{\phi}{m(m+v)}(a+2b) \quad [2b]$$

$$R0_{Lattice} = \frac{\phi}{m(m+v)}(a-4b\cos\frac{\sqrt{n}\pi}{\sqrt{n}+1}) \quad [2c]$$

136

137 For the ABM we estimate R_0 values for particular parameter combinations by treating simulation outputs as
138 ideal empirical data (Keeling & Rohani, 2008) and track the number of infections following the index case.
139 The term `base R_0' is used throughout the remainder of this paper and refers to a value of R_0 for a specific
140 pathogen phenotype in a least intensified apiary, an array with nine colonies (see Fig. 2). We determine how
141 intensification affects R_0 by separating R_0 into a 'base R_0' and an 'additional R_0'. The term 'additional R_0'
142 refers to the observed difference in R_0 for a given pathogen phenotype when comparing a 'lower intensity'
143 apiary to a 'high intensity' one (Fig. 2)

144 An extreme, but plausible, example of intensification is used for these comparisons. Specifically, an increase
145 in colonies per apiary from 9 to 225 colonies, a change to a lattice configuration, and a tenfold increase in
146 between-colony infection (0.015 to 0.15 per bee per day), demonstrated in Fig. 2. The difference in the R_0
147 before and after intensification is how we estimate 'additional R_0'. This permits the interaction (non-
148 additive) effects of our three aspects of intensification. The 'additional R_0' can then be used in combination
149 with the analytically derived relationship between R_0 and prevalence (see model [1] and equations [2a-c]) to
150 characterise how intensification affects disease prevalence. We focus on disease prevalence as both models
151 show rapid pathogen spread across apiaries, such that infection prevalence at the endemic equilibrium was
152 the major result differentiating modelling scenarios (S.I. Figs. S4 & S5).

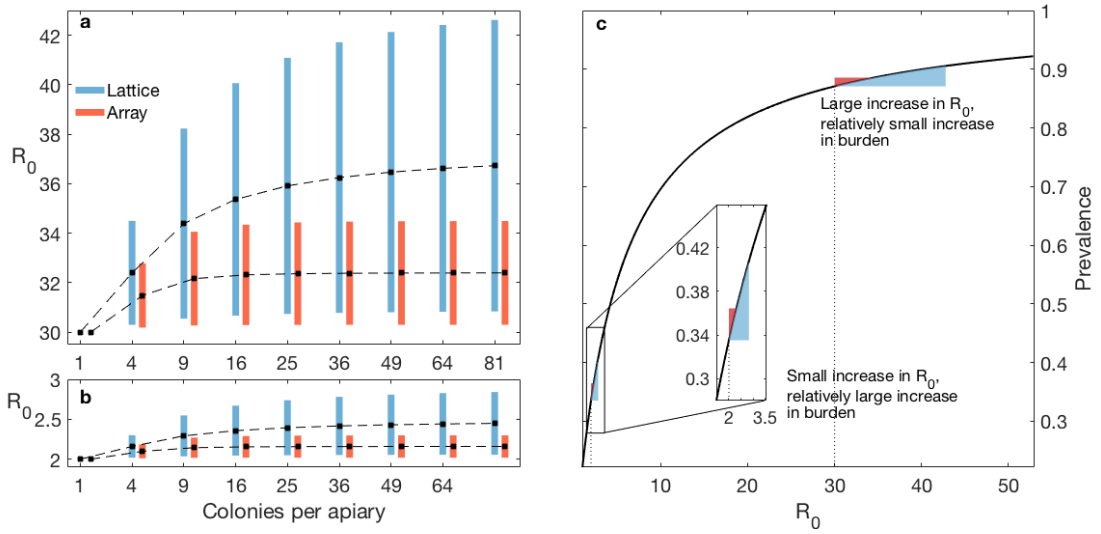


153 **Figure 2.** Illustrative schematic of the 'intensification' treatment as it is used in parts of this manuscript. We show the
154 apiary used to estimate 'base R_0' (left) compared to the intensified apiary (right) reflecting an increase in number of
155 colonies from 9 to 225, a change from an array to a lattice, and a tenfold increase in movement of honeybees between
156 colonies (illustrated using arrow weight) from a likelihood of 0.015 per bee per day to 0.15. Note that for the intensified
157 apiary, not all 225 colonies are shown, with missing colonies denoted by ellipses (...).

158

159 # Results

160 Our main results constitute three main characterisations of this system: the relationship between R_0 and
161 pathogen prevalence; the effects of intensification on R_0; and by combination of these relationships, the
162 effect of intensification on pathogen prevalence. The relationship between R_0 and pathogen prevalence is
163 principally derived from the analytical model (presented first in these results) but is confirmed to broadly
164 agree with the agent-based model (presented second). The relationship between intensification and R_0 is
165 principally derived from the ABM, presented second, but is partly explored in the analytical model presented
166 first. The critical overall result is the combination of these relationships, presented last and visualised in Fig.
167 5, demonstrating how intensification impacts disease prevalence. Detailed derivation, exploration, and
168 testing of both models is detailed in the Supplementary Information.



169

170 **Figure 3:** Relationships between number of colonies, R_0, and prevalence from model (1). Figures 3a and 3b demonstrate
171 that the effect on R_0 for different degrees of intensification rapidly asymptotes, justifying our 'single intensification'
172 treatment (Fig. 2). Figure 3c defines the relationship between R_0 and prevalence, the shape of which critically
173 determines our main result (see Fig. 5). Technical description: **a)** When R_0=30 for a single colony-apiary, the addition of
174 colonies yields a maximum increase in R_0 of 12.7 for the lattice and 4.5 for the array. **b)** When R_0=2 for a single colony,
175 there is a maximum increase in R_0 of 0.85 for the lattice and 0.29 for the array, when colonies are added. Recall that the
176 R_0 for the circle is independent of *n* (see [2b]), and hence absent from the figure. Parameter values are set to: v=0.1,
177 m=0.0272, ϕ=1600 and in a) $a+b = 4.32485\text{x}10^{-6}$ and in b) $a+b = 6.48725\text{x}10^{-5}$. The transmissibility is what affects base
178 R_0. Black dots are values where between-colony transmission is held at 10% of total transmission, with the bottom and
179 top of the bars representing 1% and 20% of the total transmission being between hives, 'b', respectively. **c)** The
180 relationship between R_0 and disease prevalence. The range of R_0 values is generated by varying the overall transmission
181 rate (i.e. $a+b$) from $2.143\text{x}10^{-6}$ to $1.178\text{x}10^{-4}$ as reported by Roberts & Hughes (2015) for *Nosema ceranae.*

182

183 Both model [1] and the ABM simulations show that, for a given number of colonies per apiary, R_0 is always
184 greatest for the lattice arrangement — the most highly connected configuration. As the number of colonies
185 per apiary increases (increasing *n*), the values of R_0 in both the array and lattice configurations increase (Fig.
186 3a & 3b), while the R_0 for the circular configuration remains unchanged (see R_0 equations). The increase in R_0
187 from the addition of colonies asymptotes quickly due to convergence in the mean number of neighbours
188 across the apiary; this is also why the R_0 for the circular apiary is independent of number of colonies as the
189 number of neighbours per colony remains two. This explains why R_0 for an array arrangement approaches
190 the R_0 value for a circular arrangement as the number of colonies increases.

191 If R_0>1, the pathogen will rapidly invade (see S.I. Section 1 &, Fig. S5) and each colony will reach a stable
192 population size and infection prevalence, called the endemic equilibrium (See S.I. Section 1). Mathematically

193 the disease prevalence at equilibrium for colony *j* is $I_j^*/(I_j^*+S_j^*)$, where S_j^* is the number of susceptible

194 honeybees and I_j^* is the number of infectious honeybees in colony *j* at equilibrium. The endemic equilibrium

195 for the circular configuration model can be solved explicitly (see S.I. Section 1). Due to symmetry, all colonies

196 within the circular apiary have disease prevalence at the endemic equilibrium of:

197 $$\frac{\phi(a+2b)-m(m+v)}{\phi(a+2b)+v(m+v)}$$

198 We can approximate the endemic equilibrium for the lattice and array configured models using perturbation

199 theory, assuming $0 < b \ll 1$ (See S.I. Section 1). The approximate disease prevalence in colony *j* at

200 equilibrium for a colony in the array or lattice configurations is:

201 $$\frac{\phi a^2 + lbm(m+v)}{\phi a^2 + a(m+v)^2 - blv(m+v)}$$

202 where *l* is the number of neighbours that colony *j* has. For any given set of parameters, we can therefore

203 formulate both R_0 and prevalence, allowing us to characterise the relationship shown in Fig. 3c.

204 We show analytically, and in the ABM (S.I. Section 3) that intensification in the form of an increase in

205 colonies or an increase in movement between colonies increases R_0 (Fig. 3a & 3b). Figure 4b shows the

206 additional R_0 caused by our most extreme plausible changes in apiary management. The change in R_0 caused

207 by increasing apiary size rapidly asymptotes (Fig. 3 a & b).

208 The effect of intensification is dependent on the base R_0 – for small base R_0, intensification causes little

209 additional R_0, but at intermediate or high base R_0, intensification leads to large additional R_0 (Fig. 4b). While

210 the increase in R_0 is largest for an already large base R_0, this relationship saturates and the relative increase

211 in R_0 for a given base R_0 stays relatively constant for large base R_0 values. The relationship shows a strong

212 nonlinearity when examining all three aspects of intensification in combination.

213

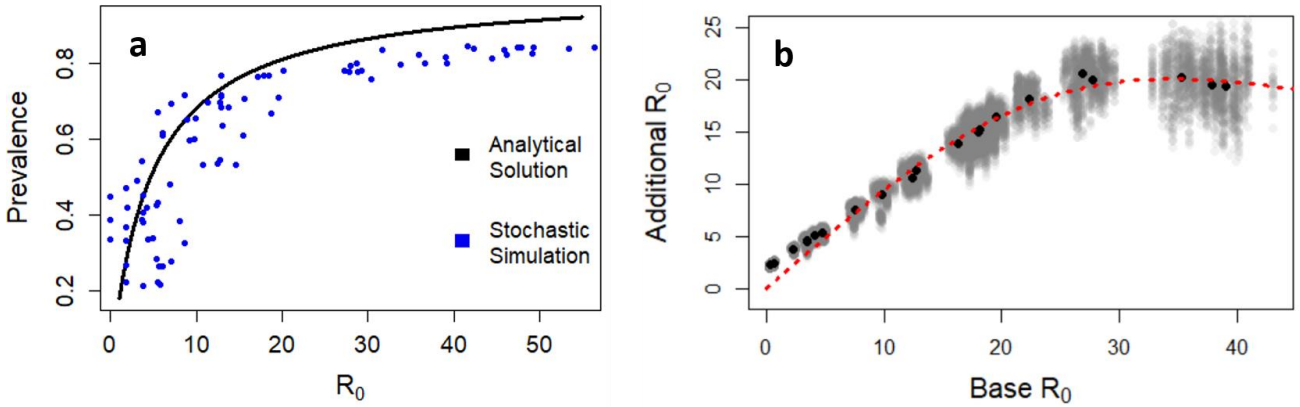


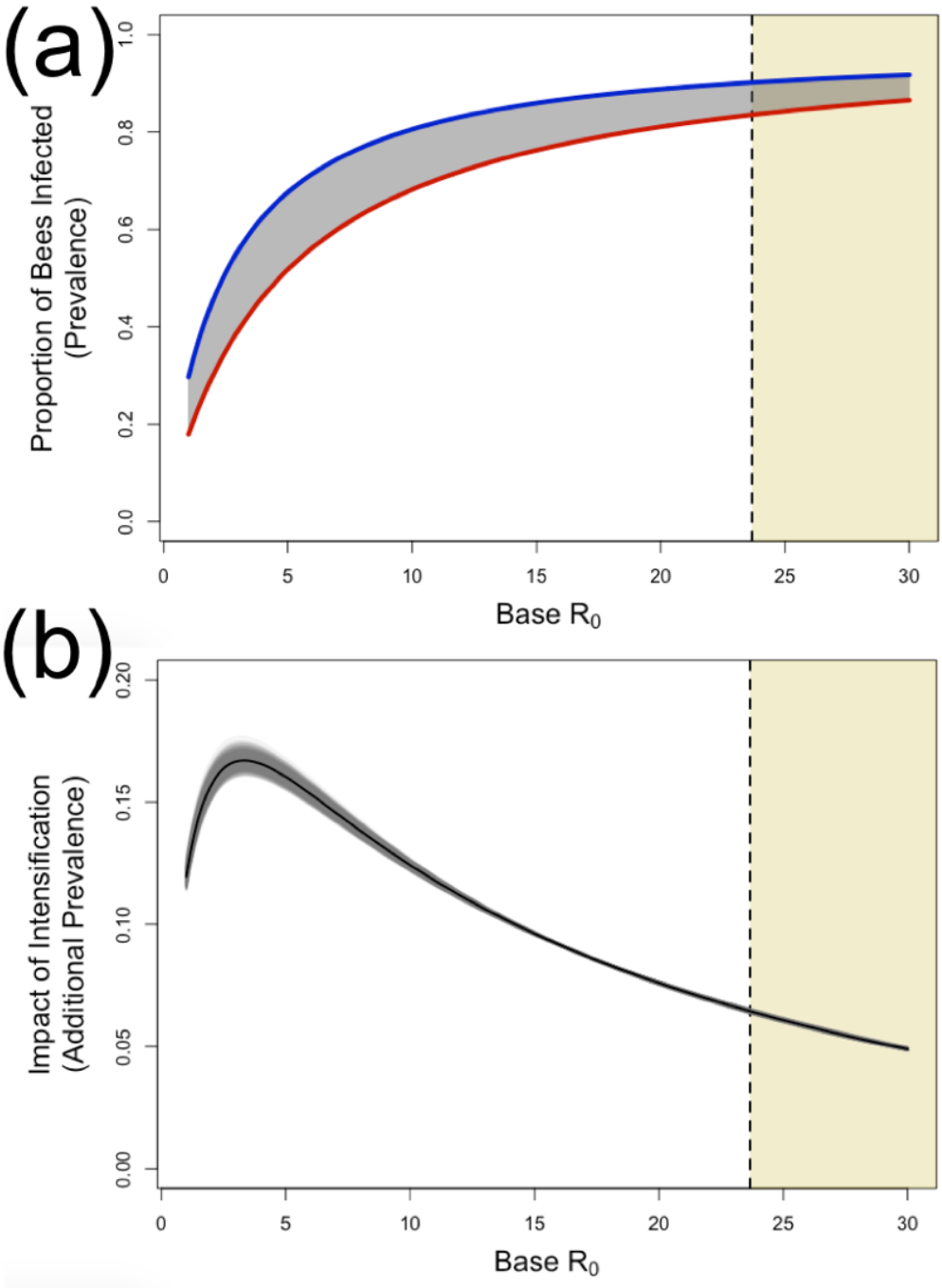
Figure 4: Results from the ABM. Figure 4a demonstrates the agreement between the ABM and analytical model; figure 4b presents the critical relationship estimated from the ABM relating base R_0 to the increase in R_0 following intensification (see Fig. 2), the shape of which critically determines our main result (see Fig. 5). Technical description: **a)** shows agreement between the stochastic simulations (ABM) and analytical model (Fig. 3c); using the following equivalent model parameterisation to that for Fig. 3c: Circular configuration, $n = 9$, $M = 58200$, $\phi = 1600$, $5x10^{-6} \leq \beta \leq 1x10^{-4}$, $\nu = 0.1$, $\rho = 0.1$ (see S.I. Section 2). **b)** examines how an extreme example of intensification (see Fig. 2) alters R_0 across a range of different 'base R_0' values determined by pathogen phenotype using the ABM. Grey points represent individual simulation comparisons, black points represent mean values. Base R_0 values are unevenly distributed across the range due to R_0 being an emergent property of the system in both plot panels. We derive a non-linear relationship between 'base R_0' and 'additional R_0' for panel **b**, corresponding to Fig. 2 (see Fig. 2 for panel **b** parameterisation, otherwise as listed for **a**, plotted as a dashed red line. Variation within clusters is a result of the stochastic simulations.

By understanding the effect of intensification on R_0 (Fig. 4b) and by characterising the relationship between R_0 and disease prevalence (Fig. 3c, Fig. 4a), we can show how intensification impacts disease prevalences. We approximate the non-linear relationship between 'base R_0' (pathogen phenotype) and the 'additional R_0' (effect of intensification) in Fig. 4b. We use a bootstrapping approach to create 1000 subsamples (subsample size = 10% of full sample with replacement) of our combined approach. Each subsample is used to generate a non-linear model of the form $y = ax / (b + x^c)$, where y is 'additional R_0' and x is 'base R_0', using a nonlinear least squares approach in R (v 3.3.1). The relationship generated using the full sample is plotted in Fig. 4b.

We combine this relationship characterising how base R_0 affects intensified additional R_0 (Fig. 4b) with the derived relationship between R_0 and pathogen prevalence shown in Fig. 3c, allowing us to predict how intensification impacts prevalences (Fig. 5). Fig. 5a shows the proportion of bees infected by a given (base R_0) pathogen for the two apiaries in Fig. 2. The difference in disease prevalence between these lines is the impact of intensification and is plotted in Fig. 5b. Fig. 5b shows a distinctly peaked relationship between base

239 R_0 and the impact of intensification, with the impact of intensification peaking around base R_0 = 3.3, and
240 then rapidly declining. Even at its peak, the effect of intensification (which is as extreme as plausible), leads
241 to an additional ~18% of bees infected at disease equilibrium. We present figure 5 as a the most important
242 graphic for understanding the overall conclusions of this study, as the apparent 'small' shift in R_0 required to
243 double prevalence (Fig. 3c and 4a) is actually very difficult to achieve for low R_0 pathogens (see Fig. 3b, 4b),
244 resulting in the 'maximum plausible' change shown by the peak in Fig. 5b (~18.5%).

245 We contextualize these results by calculating an estimate of the lower-bound of R_0 value for a honeybee
246 pathogen (see highlighted regions in Fig. 5). We identified this region based on empirical data for the
247 microsporidian pathogen *Nosema ceranae*; this was the only pathogen for which experimentally derived
248 transmission rates as well as robust information on mortality due to infection is available (Martín-Hernández
249 et al., 2011; Paxton, Klee, Korpela, & Fries, 2007; Roberts & Hughes, 2015). To estimate the plausible R_0
250 boundary in our model for this pathogen, we parameterised our mathematical model using the lowest
251 empirically supported transmission value with the highest supported additional mortality, and fixed
252 movement of honeybees between colonies at its lowest supported natural rate (Currie & Jay, 1991). We
253 then calculated the R_0 for a circular apiary due to its scale independence.



254

255 **Figure 5**: Depictions of our critical finding characterising the maximum (peak), and likely (shaded region),
256 increases in prevalence of a pathogen following local intensification of apiculture. High prevalence even in 'low
257 intensity' (see Fig. 2) systems yields little opportunity for large increases in prevalence. Panel **(a)** shows the
258 proportion of bees infected (prevalence) in non-intensified apiaries (lower red line) compared to intensified
259 apiaries (upper blue line), take from the mean values derived in Fig. 4b and the relationship shown in Fig. 3c.
260 The shaded grey area between these curves is the additional prevalence caused by intensification – the
261 'impact of intensification'. This is plotted in panel **(b)** where the black line represents the mean relationship,
262 and the grey lines represent 1000 bootstrapped samples. The vertical dashed line and yellow-shaded region of
263 the graphs to the right of the dashed line show a lowest estimated value of R_0 for *Nosema ceranae*. Figures
264 start at $R_0 = 1.0008$.

Discussion

Our results present a counterintuitive picture of apicultural intensification and its consequences on disease prevalence within apiaries. Even in their most plausibly extreme cases, changes in the number of colonies, their spatial arrangement, and transmission rates between colonies (reflecting management intensification (Brosi et al., 2017)) had only a small effect on the severity of disease at the apiary level for pathogens of interest. Apicultural intensification leads to large gains in R_0 when R_0 is initially high and small gains in R_0 when R_0 is initially low (Fig. 4b). However, increases in R_0 cause large increases in prevalence only when R_0 is initially low (Fig. 3c, 4a). Pathogens with a base $R_0 \approx 3$ benefit most from intensification in terms of increased prevalence (Fig. 5); As discussed below, we argue that there is likely to be a high base R_0 in important honeybee diseases and therefore our models suggest that there is likely to be little effect of apiary-scale intensification on disease prevalences. However, if a pathogen emerges with a relatively low R_0, our model does indicate that extreme intensification could lead to a significant increase in prevalence of approximately 18.5%. Therefore, if intensification increases the risk of novel pathogen emergence, then these newly emerged pathogens would benefit from intensification, as it would significantly increase their disease prevalence, relative to the pre-intensified apiary.

Our models most closely resemble the ecology of a directly transmitted microparasite able to infect individual honeybees at any life stage, conceptually similar to the microsporidian pathogens *Nosema* spp. (Fantham & Porter, 1912). *Nosema* is a major concern to beekeepers worldwide (Higes et al., 2008, 2009; Paxton, 2010), and has a minimum estimated base R_0 of 23 (Fig. 5) when modelled here. We found that apicultural intensification, in the context of a pathogen with an initial R_0 of 23, leads to a maximum 6.6% increase in disease prevalence. Our models predicted disease prevalences of up to 90% (Fig. 3, Fig. 5; S.I. Section 3), which while high, are empirically supported for the honeybee system (Higes et al., 2008; Kielmanowicz et al., 2015), and feature in other modelling studies that use similar transmission parameters to ours (Betti, Wahl, & Zamir, 2014). *Nosema* was the only

290 pathogen for which there are direct empirical studies characterising its transmissibility, however,
291 other honeybee pathogens such as deformed wing virus are also well studied. While estimating an
292 R_0 for DWV is difficult due to active management by beekeepers, maximum reported prevalences
293 that may be indicative of its true 'unmanaged' R_0 are high, for example 73% in Natsopoulou et al.
294 (2017), 80% in Budge et al. (2015), and 100% in Stamets et al. (2018). These high prevalences are
295 consistent with high R_0 values (Fig. 3c, Fig. 4a, & S.I. (Section 3)).

296 We additionally explored the behaviour of a more specific model, using an age-structured approach
297 to infection dynamics, where only larvae are vulnerable to infection and develop into infectious
298 adults with a high pathogen-associated mortality (as might be appropriate for pathogens such as the
299 acute paralysis virus complex (Martin, 2001)), presented in the S.I. (Section 3). Convergence to
300 equilibrium happens more slowly than the main model presented here, but still occurs quickly
301 (within a single beekeeping season; see S.I. 3 Fig. S7). However adult-bee infection prevalence is far
302 lower than seen in our SI model (S.I. Fig. S7) – this is in agreement with observations of lower
303 prevalence of paralysis viruses (Budge et al., 2015). Notably, the endemic equilibrium prevalence
304 increases only by small magnitudes as movement between colonies or apiary sizes are drastically
305 increased (S.I. Fig. S7), in agreement with our main general result. This equivalence in behaviour
306 between different models reflecting large disparities in infection mechanics and different endemic
307 prevalences demonstrates that these results are likely generalisable to many honeybee pathogens.

308 We find rapid spread of a given pathogen across an apiary, which quickly reaches endemic
309 equilibrium (S.I. Figs. S4-S6). While pathogens with a higher R_0 reach this equilibrium more quickly,
310 there is universally rapid spread. Given this result, we mainly focussed on the disease prevalence
311 experienced at endemic equilibrium. Despite assuming transmission only to nearest neighbours,
312 pathogen spread occurs rapidly, and the nearest neighbour assumption alters this very little when
313 removed or relaxed (see S.I. Fig. S6). The rate at which epidemics are established in our model is also
314 in agreement with other honeybee pathogen models. For example, Jatulan, Rabajante, Banaay,

315 Fajardo, & Jose (2015) show a single infectious adult causes an American Foulbrood (*Paenibacillus*
316 *larvae*) epidemic that peaks within 50 days. Whilst they do not explicitly find an R_0 for *P. larvae*, the
317 short timescales characterising their epidemics are in line with ours (S.I. Section 3), suggesting high
318 R_0 values and that their model would behave similarly to ours at an apiary scale.

319 Our inter-colony transmission can be understood to capture multiple processes arriving from
320 beekeeper management such as brood transplantation or reduced distance between colonies (Brosi
321 et al., 2017) as well as recognised transmission routes such as honeybee drift (Jay, 1965). Our
322 approach was informed by studies which have focussed on how changes in the number of colonies
323 and apiary configurations (Jay, 1966, 1968) alter drift (Dynes et al., 2017). Links between drift-
324 mediated pathogen transmission and colony numbers have been documented for a variety of
325 pathogens (Seeley & Smith, 2015) – including brood specialised and non-specialised, micro- and
326 macro- parasites (Belloy et al., 2007; Budge et al., 2010; Dynes et al., 2017; Nolan & Delaplane,
327 2017). Larger numbers of colonies per apiary are a driver of higher drift (Currie & Jay, 1991), as are
328 changes in apiary arrangement (Jay, 1966; Dynes, Berry, Delaplane, Brosi, & Roode, 2019). While
329 beekeepers typically maintain equal distances between their colonies regardless of how many
330 colonies are in the apiary (such that larger apiaries have a bigger area footprint), our approach of
331 increasing between-colony transmission in larger apiaries would also capture any additional
332 transmission from spatial crowding.

333 Two clear candidates for future development of this model include seasonality and demography,
334 which are closely linked. Honeybee demography within a colony influences epidemiology (Betti,
335 Wahl, & Zamir, 2016) due in part to the temporal polyethism of task allocation influencing exposure
336 and immunity (Calderone & Page, 1996), as well as the flexible ability of honeybees to regain
337 immune function when they revert roles (Amdam et al., 2005; Robinson, Page, Strambi, & Strambi,
338 1992). However, patterns in how age and immunosenescence in honeybees relates to survival and
339 infectiousness remain complicated (Roberts & Hughes, 2014). Analytically tractable models

accounting for the role of this complex demography in understanding stress in a colony have only recently been developed (Booton, Iwasa, Marshall, & Childs, 2017), and extending these models to incorporate diseases at the apiary scale is challenging. However, notable phenomena worth pursuing include: the role of male bees, which are known to be more easily infected, more infectious, and more likely to drift between colonies (Currie & Jay, 1991; Roberts & Hughes, 2015); as well as the role of robbing – where honeybees invade other colonies to steal food (Fries & Camazine, 2001; Lindström, Korpela, & Fries 2008).

At broader scales, overstocking of colonies may lead to resource limitation and consequently impaired immune function (Al-Ghamdi, Adgaba, Getachew, & Tadesse, 2016; Pasquale et al., 2013). These effects are important for a broader understanding of honeybee epidemiology, but should be separated from the within-apiary processes studied here. Additionally, most honeybee infectious diseases are caused by multi-host pathogens shared with other wild bees (Fürst et al., 2014; Manley et al., 2015; McMahon et al., 2015, 2018). Honeybee colony density across a landscape therefore has implications for wild pollinator health (Cohen et al., 2017; Graystock et al., 2016), however our results suggest that increased stocking of honeybees may have smaller impacts on local pollinator infectious disease dynamics than may have been previously thought.

Other industrialised agricultural livestock systems reflect extreme host densities similar to those in this study. However, the R_0 for honeybee diseases may exceed that of other livestock diseases. We compare our lower threshold estimate for the R_0 of *N. ceranae* to all available R_0 values for livestock diseases that we could readily find in the literature (Fig. S9, see S.I. Section 4). Notably, all other livestock diseases for which R_0 estimates exist show minimum R_0 values far below our honeybee estimate, however examples of agricultural R_0 values as high or higher than those we present for honeybees do also exist. There is therefore a clear need to develop explicit models of agricultural intensification scenarios for important agricultural disease.

Overall, our findings represent the first stage in developing robust epidemiological models for studying honeybee pathogens at an apiary scale. In the face of increasing challenges to global apiculture, our models predict that the size of apiaries *per se* is not causing notable increases in disease prevalence for important established bee pathogens, while it may increase the risk of pathogen emergence. Finally, this study demonstrates that conventional thought on how agricultural intensification influences disease may not be robust in the face of system-specific ecological nuance.

Acknowledgements

LJB acknowledges funding from a Natural Environment Research Council training grant (NE/L002434/1). CR, MB, and AW acknowledge funding from a Biotechnology and Biological Sciences Research Council grant (BB/L010879/1). BJB, JCdR and KSD acknowledge funding from National Institutes of Health (R01-109501); the content of this study is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Authors' Contributions

All authors contributed to conceptualisation and scope definition of the study. LJB, CR, MB developed approach. Mathematical modelling was undertaken by CR, AW, and MB. Computational modelling by LJB, KD, and MB. Model scope and parameterisation by LJB, KD, JCdR, BJB, LW. LJB and CR created figures, interpreted results and drafted manuscript with guidance and input from all authors. All authors contributed to further drafting, revision, and finalisation. All authors approved the final version for publication.

Data Accessibility

The agent-based model is made available in association with this manuscript via Dryad Digital Repository doi:10.5061/dryad.rn2j5p0 (Bartlett et al. 2019).

References

388 Al-Ghamdi, A., Adgaba, N., Getachew, A., & Tadesse, Y. (2016). New approach for determination of
389 an optimum honeybee colony's carrying capacity based on productivity and nectar secretion
390 potential of bee forage species. *Saudi Journal of Biological Sciences*, *23*(1), 92–100.
391 doi:10.1016/j.sjbs.2014.09.0209
392 Amdam, G. V., Aase, A. L. T. O., Seehuus, S.-C., Kim Fondrk, M., Norberg, K., & Hartfelder, K. (2005).
393 Social reversal of immunosenescence in honey bee workers. *Experimental Gerontology*,
394 *40*(12), 939–947. doi:10.1016/j.exger.2005.08.004
395 Anderson, R. M., & May, R. M. (1992). *Infectious diseases of humans: dynamics and control* (Vol. 28).
396 Wiley Online Library.
397 Atkins, K. E., Read, A. F., Savill, N. J., Renz, K. G., Islam, A. F., Walkden-Brown, S. W., & Woolhouse,
398 M. E. J. (2013). Vaccination and Reduced Cohort Duration Can Drive Virulence Evolution:
399 Marek's Disease Virus and Industrialized Agriculture. *Evolution*, *67*(3), 851–860.
400 doi:10.1111/j.1558-5646.2012.01803.x
401 Bartlett, L. J., Rozins, C., Brosi, B. J., Delaplane, K. S., de Roode, J. C., White, A., Wilfert, L., Boots, M.
402 (2019) Data files: ABM Simulation Code from: Industrial bees: the impact of apicultural
403 intensification on local disease prevalence. Dryad Digital Repository
404 doi:10.5061/dryad.rn2j5p0
405 Becher, M. A., Osborne, J. L., Thorbek, P., Kennedy, P. J., & Grimm, V. (2013). REVIEW: Towards a
406 systems approach for understanding honeybee decline: a stocktaking and synthesis of
407 existing models. *Journal of Applied Ecology*, *50*(4), 868–880. doi:10.1111/1365-2664.12112
408 Belloy, L., Imdorf, A., Fries, I., Forsgren, E., Berthoud, H., Kuhn, R., & Charrière, J.-D. (2007). Spatial
409 distribution of Melissococcus plutonius in adult honey bees collected from apiaries and
410 colonies with and without symptoms of European foulbrood. *Apidologie*, *38*(2), 136–140.
411 Betti, M. I., Wahl, L. M., & Zamir, M. (2016). Age structure is critical to the population dynamics and
412 survival of honeybee colonies. *Royal Society Open Science*, *3*(11), 160444.
413 doi:10.1098/rsos.160444

414 Betti, Matt I., Wahl, L. M., & Zamir, M. (2014). Effects of Infection on Honey Bee Population
415 Dynamics: A Model. *PLOS ONE*, *9*(10), e110237. doi:10.1371/journal.pone.0110237
416 Booton, R. D., Iwasa, Y., Marshall, J. A. R., & Childs, D. Z. (2017). Stress-mediated Allee effects can
417 cause the sudden collapse of honey bee colonies. *Journal of Theoretical Biology*, *420*, 213–
418 219. doi:10.1016/j.jtbi.2017.03.009
419 Brijnath, B., Butler, C. D., & McMichael, A. J. (2014). In an interconnected world: joint research
420 priorities for the environment, agriculture and infectious disease. *Infectious Diseases of*
421 *Poverty*, *3*, 2. doi:10.1186/2049-9957-3-2
422 Brosi, B. J., Delaplane, K. S., Boots, M., & de Roode, J. C. (2017). Ecological and evolutionary
423 approaches to managing honeybee disease. *Nature Ecology & Evolution*, *1*(9), 1250.
424 doi:10.1038/s41559-017-0246-z
425 Budge, G. E., Barrett, B., Jones, B., Pietravalle, S., Marris, G., Chantawannakul, P., … Brown, M. A.
426 (2010). The occurrence of Melissococcus plutonius in healthy colonies of Apis mellifera and
427 the efficacy of European foulbrood control measures. *Journal of Invertebrate Pathology*,
428 *105*(2), 164–170. doi:10.1016/j.jip.2010.06.004
429 Budge, G. E., Pietravalle, S., Brown, M., Laurenson, L., Jones, B., Tomkies, V., & Delaplane, K. S.
430 (2015). Pathogens as Predictors of Honey Bee Colony Strength in England and Wales. *PLOS*
431 *ONE*, *10*(7), e0133228. doi:10.1371/journal.pone.0133228
432 Calderone, N. W., & Page, R. E. (1996). Temporal polyethism and behavioural canalization in the
433 honey bee,Apis mellifera. *Animal Behaviour*, *51*(3), 631–643. doi:10.1006/anbe.1996.0068
434 Cohen, H., Quistberg, R. D., Philpott, S. M., & DeGrandi-Hoffman, G. (2017). Vegetation Management
435 and Host Density Influence Bee–Parasite Interactions in Urban Gardens. *Environmental*
436 *Entomology*. doi:10.1093/ee/nvx155
437 Cressler, C. E., McLeod, D. V., Rozins, C., Hoogen, J. V. D., & Day, T. (2016). The adaptive evolution of
438 virulence: a review of theoretical predictions and empirical tests. *Parasitology*, *143*(7), 915–
439 930. doi:10.1017/S003118201500092X

Currie, R. W., & Jay, S. C. (1991). Drifting behaviour of drone honey bees (Apis mellifera L.) in commercial apiaries. *Journal of Apicultural Research*, *30*(2), 61–68. doi:10.1080/00218839.1991.11101235

De la Rúa, P., Jaffé, R., Dall'Olio, R., Muñoz, I., & Serrano, J. (2009). Biodiversity, conservation and current threats to European honeybees. *Apidologie*, *40*(3), 263–284. doi:10.1051/apido/2009027

Dynes, T. L., Roode, J. C. D., Lyons, J. I., Berry, J. A., Delaplane, K. S., & Brosi, B. J. (2017). Fine scale population genetic structure of Varroa destructor, an ectoparasitic mite of the honey bee (Apis mellifera). *Apidologie*, *48*(1), 93–101. doi:10.1007/s13592-016-0453-7

Dynes, T. L., Berry, J. A., Delaplane, K. S., Brosi, B. J., & Roode, J. C. de. (2019). Reduced density and visually complex apiaries reduce parasite load and promote honey production and overwintering survival in honey bees. *PLOS ONE*, *14*(5), e0216286. doi: 10.1371/journal.pone.0216286

Fantham, H. B., & Porter, A. (1912). The Morphology and Life History of Nosema Apis and the Significance of its Various Stages in the so-called 'Isle of Wight' Disease in Bees (Microsporidiosis). *Annals of Tropical Medicine & Parasitology*, *6*(2), 163–195. doi:10.1080/00034983.1912.11687060

Free, J. B. (1958). The drifting of honey-bees. *The Journal of Agricultural Science*, *51*(3), 294–306. doi:10.1017/S0021859600035103

Fries, I., & Camazine, S. (2001). Implications of horizontal and vertical pathogen transmission for honey bee epidemiology. *Apidologie*, *32*(3), 199–214. doi:10.1051/apido:2001122

Fürst, M. A., McMahon, D. P., Osborne, J. L., Paxton, R. J., & Brown, M. J. F. (2014). Disease associations between honeybees and bumblebees as a threat to wild pollinators. *Nature*, *506*(7488), 364. doi:10.1038/nature12977

Gandon, S., Hochberg, M. E., Holt, R. D., & Day, T. (2013). What limits the evolutionary emergence of pathogens? *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *368*(1610), 20120086. doi:10.1098/rstb.2012.0086

Ghazoul, J. (2005). Buzziness as usual? Questioning the global pollination crisis. *Trends in Ecology & Evolution*, *20*(7), 367–373. doi:10.1016/j.tree.2005.04.026

Giacobino, A., Cagnolo, N. B., Merke, J., Orellano, E., Bertozzi, E., Masciangelo, G., … Signorini, M. (2014). Risk factors associated with the presence of Varroa destructor in honey bee colonies from east-central Argentina. *Preventive Veterinary Medicine*, *115*(3–4), 280–287. doi:10.1016/j.prevetmed.2014.04.002

Goodwin, R. M., Perry, J. H., & Houten, A. T. (1994). The effect of drifting honey bees on the spread of American foulbrood infections. *Journal of Apicultural Research*, *33*(4), 209–212. doi:10.1080/00218839.1994.11100873

Graystock, P., Blane, E. J., McFrederick, Q. S., Goulson, D., & Hughes, W. O. H. (2016). Do managed bees drive parasite spread and emergence in wild bees? *International Journal for Parasitology: Parasites and Wildlife*, *5*(1), 64–75. doi:10.1016/j.ijppaw.2015.10.001

Higes, M., Martín-Hernández, R., Botías, C., Bailón, E. G., González-Porto, A. V., Barrios, L., … Meana, A. (2008). How natural infection by Nosema ceranae causes honeybee colony collapse. *Environmental Microbiology*, *10*(10), 2659–2669. doi:10.1111/j.1462-2920.2008.01687.x

Higes, M., Martín-Hernández, R., Garrido-Bailón, E., González-Porto, A. V., García-Palencia, P., Meana, A., … Bernal, J. L. (2009). Honeybee colony collapse due to Nosema ceranae in professional apiaries. *Environmental Microbiology Reports*, *1*(2), 110–113. doi:10.1111/j.1758-2229.2009.00014.x

Jacques, A., Laurent, M., Consortium, E., Ribière-Chabert, M., Saussac, M., Bougeard, S., … Chauzat, M.-P. (2017). A pan-European epidemiological study reveals honey bee colony survival depends on beekeeper education and disease control. *PLOS ONE*, *12*(3), e0172591. doi:10.1371/journal.pone.0172591

James, C. (1981). The cost of disease to world agriculture. *Seed Science and Technology (Netherlands)*. Retrieved from http://agris.fao.org/agris-search/search.do?recordID=XE8280339

Jatulan, E. O., Rabajante, J. F., Banaay, C. G. B., Fajardo, A. C., & Jose, E. C. (2015). A Mathematical Model of Intra-Colony Spread of American Foulbrood in European Honeybees (Apis mellifera L.). *PLOS ONE*, *10*(12), e0143805. doi:10.1371/journal.pone.0143805

Jay, S. C. (1965). Drifting of Honeybees in Commercial Apiaries 1. Effect of Various Environmental Factors. *Journal of Apicultural Research*, *4*(3), 167–175. doi:10.1080/00218839.1965.11100119

Jay, S. C. (1966). Drifting of Honeybees in Commercial Apiaries. III. Effect of Apiary Layout. *Journal of Apicultural Research*, *5*(3), 137–148. doi:10.1080/00218839.1966.11100147

Jay, S. C. (1968). Drifting of Honeybees in Commercial Apiaries. IV. Further Studies of the Effect of Apiary Layout. *Journal of Apicultural Research*, *7*(1), 37–44. doi:10.1080/00218839.1968.11100185

Jones, B. A., Grace, D., Kock, R., Alonso, S., Rushton, J., Said, M. Y., … Pfeiffer, D. U. (2013). Zoonosis emergence linked to agricultural intensification and environmental change. *Proceedings of the National Academy of Sciences*, *110*(21), 8399–8404. doi:10.1073/pnas.1208059110

Keeling, M. J., & Rohani, P. (2008). *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press.

Kennedy, D. A., Kurath, G., Brito, I. L., Purcell, M. K., Read, A. F., Winton, J. R., & Wargo, A. R. (2016). Potential drivers of virulence evolution in aquaculture. *Evolutionary Applications*, *9*(2), 344–354. doi:10.1111/eva.12342

Kielmanowicz, M. G., Inberg, A., Lerner, I. M., Golani, Y., Brown, N., Turner, C. L., … Ballam, J. M. (2015). Prospective Large-Scale Field Study Generates Predictive Model Identifying Major Contributors to Colony Losses. *PLOS Pathogens*, *11*(4), e1004816. doi:10.1371/journal.ppat.1004816

516 Lindström, A., Korpela, S., & Fries, I. (2008). Horizontal transmission of Paenibacillus larvae spores
517 between honey bee (Apis mellifera) colonies through robbing. *Apidologie*, *39*(5), 515–522.
518 doi:10.1051/apido:2008032
519 Manley, R., Boots, M., & Wilfert, L. (2015). REVIEW: Emerging viral disease risk to pollinating insects:
520 ecological, evolutionary and anthropogenic factors. *Journal of Applied Ecology*, *52*(2), 331–
521 340. doi:10.1111/1365-2664.12385
522 Martin, S. J. (2001). The role of Varroa and viral pathogens in the collapse of honeybee colonies: a
523 modelling approach. *Journal of Applied Ecology*, *38*(5), 1082–1093. doi:10.1046/j.1365-
524 2664.2001.00662.x
525 Martín-Hernández, R., Botías, C., Barrios, L., Martínez-Salvador, A., Meana, A., Mayack, C., & Higes,
526 M. (2011). Comparison of the energetic stress associated with experimental Nosema
527 ceranae and Nosema apis infection of honeybees (Apis mellifera). *Parasitology Research*,
528 *109*(3), 605–612. doi:10.1007/s00436-011-2292-9
529 McMahon, D. P., Fürst, M. A., Caspar, J., Theodorou, P., Brown, M. J. F., & Paxton, R. J. (2015). A sting
530 in the spit: widespread cross-infection of multiple RNA viruses across wild and managed
531 bees. *Journal of Animal Ecology*, *84*(3), 615–624. doi:10.1111/1365-2656.12345
532 McMahon, D. P., Wilfert, L., Paxton, R. J., & Brown, M. J. F. (2018). Emerging Viruses in Bees: From
533 Molecules to Ecology. In *Advances in Virus Research*. Academic Press.
534 doi:10.1016/bs.aivir.2018.02.008
535 Mennerat, A., Nilsen, F., Ebert, D., & Skorping, A. (2010). Intensive Farming: Evolutionary
536 Implications for Parasites and Pathogens. *Evolutionary Biology*, *37*(2–3), 59–67.
537 doi:10.1007/s11692-010-9089-0
538 Mõtus, K., Raie, A., Orro, T., Chauzat, M.-P., & Viltrop, A. (2016). Epidemiology, risk factors and
539 varroa mite control in the Estonian honey bee population. *Journal of Apicultural Research*,
540 *55*(5), 396–412. doi:10.1080/00218839.2016.1251081

541 Natsopoulou, M. E., McMahon, D. P., Doublet, V., Frey, E., Rosenkranz, P., & Paxton, R. J. (2017). The
542 virulent, emerging genotype B of Deformed wing virus is closely linked to overwinter
543 honeybee worker loss. *Scientific Reports*, *7*(1), 5242. doi:10.1038/s41598-017-05596-3
544 Neumann, P., Radloff, S. E., Pirk, C. W. W., & Hepburn, R. (2003). The behaviour of drifted Cape
545 honeybee workers (Apis mellifera capensis): predisposition for social parasitism? *Apidologie*,
546 *34*(6), 585–590. doi:10.1051/apido:2003048
547 Nolan, M. P., & Delaplane, K. S. (2017). Distance between honey bee Apis mellifera colonies
548 regulates populations of Varroa destructor at a landscape scale. *Apidologie*, *48*(1), 8–16.
549 doi:10.1007/s13592-016-0443-9
550 Pacini, A., Giacobino, A., Molineri, A., Bulacio Cagnolo, N., Aignasse, A., Zago, L., … Signorini, M.
551 (2016). Risk factors associated with the abundance of Nosema spp. in apiaries located in
552 temperate and subtropical conditions after honey harvest. *Journal of Apicultural Research*,
553 *55*(4), 342–350. doi:10.1080/00218839.2016.1245396
554 Pasquale, G. D., Salignon, M., Conte, Y. L., Belzunces, L. P., Decourtye, A., Kretzschmar, A., … Alaux, C.
555 (2013). Influence of Pollen Nutrition on Honey Bee Health: Do Pollen Quality and Diversity
556 Matter? *PLOS ONE*, *8*(8), e72016. doi:10.1371/journal.pone.0072016
557 Paxton, R. J. (2010). Does infection by Nosema ceranae cause “Colony Collapse Disorder” in honey
558 bees (Apis mellifera)? *Journal of Apicultural Research*, *49*(1), 80–84.
559 doi:10.3896/IBRA.1.49.1.11
560 Paxton, R. J., Klee, J., Korpela, S., & Fries, I. (2007). Nosema ceranae has infected Apis mellifera in
561 Europe since at least 1998 and may be more virulent than Nosema apis. *Apidologie*, *38*(6),
562 558–565. doi:10.1051/apido:2007037
563 Pocol, C. B., Marghitas, L. A., & Popa, A. A. (2012). Evaluation of sustainability of the beekeeping
564 sector in the North West Region of Romania. *J Food Agric Environ*, *10*, 1132–1138.

565 Potts, S. G., Biesmeijer, J. C., Kremen, C., Neumann, P., Schweiger, O., & Kunin, W. E. (2010). Global
566 pollinator declines: trends, impacts and drivers. *Trends in Ecology & Evolution*, *25*(6), 345–
567 353. doi:10.1016/j.tree.2010.01.007
568 Roberts, K. E., & Hughes, W. O. H. (2015). Horizontal transmission of a parasite is influenced by
569 infected host phenotype and density. *Parasitology*, *142*(2), 395–405.
570 Roberts, Katherine E., & Hughes, W. O. H. (2014). Immunosenescence and resistance to parasite
571 infection in the honey bee, Apis mellifera. *Journal of Invertebrate Pathology*, *121*, 1–6.
572 doi:10.1016/j.jip.2014.06.004
573 Robinson, G. E., Page, R. E., Strambi, C., & Strambi, A. (1992). Colony Integration in Honey Bees:
574 Mechanisms of Behavioral Reversion. *Ethology*, *90*(4), 336–348. doi:10.1111/j.1439-
575 0310.1992.tb00844.x
576 Roetschi, A., Berthoud, H., Kuhn, R., & Imdorf, A. (2008). Infection rate based on quantitative real-
577 time PCR of Melissococcus plutonius, the causal agent of European foulbrood, in honeybee
578 colonies before and after apiary sanitation. *Apidologie*, *39*(3), 362–371.
579 doi:10.1051/apido:200819
580 Rozins, C., & Day, T. (2016). Disease eradication on large industrial farms. *Journal of Mathematical*
581 *Biology*, *73*(4), 885–902. doi:10.1007/s00285-016-0973-9
582 Seeley, T. D., & Smith, M. L. (2015). Crowding honeybee colonies in apiaries can increase their
583 vulnerability to the deadly ectoparasite Varroa destructor. *Apidologie*, *46*(6), 716–727.
584 doi:10.1007/s13592-015-0361-2
585 Stamets, P. E., Naeger, N. L., Evans, J. D., Han, J. O., Hopkins, B. K., Lopez, D., … Sheppard, W. S.
586 (2018). Extracts of Polypore Mushroom Mycelia Reduce Viruses in Honey Bees. *Scientific*
587 *Reports*, *8*(1), 13936. doi:10.1038/s41598-018-32194-8
588 van den Driessche, P., & Watmough, J. (2002). Reproduction numbers and sub-threshold endemic
589 equilibria for compartmental models of disease transmission. *Mathematical Biosciences*,
590 *180*(1), 29–48. doi:10.1016/S0025-5564(02)00108-6

van Engelsdorp, D., Lengerich, E., Spleen, A., Dainat, B., Cresswell, J., Baylis, K., … Saegerman, C. (2013). Standard epidemiological methods to understand and improve Apis mellifera health. *Journal of Apicultural Research*, *52*(4), 1–16. doi:10.3896/IBRA.1.52.4.15

vanEngelsdorp, D., & Meixner, M. D. (2010). A historical review of managed honey bee populations in Europe and the United States and the factors that may affect them. *Journal of Invertebrate Pathology*, *103*, S80–S95. doi:10.1016/j.jip.2009.06.011

Wilfert, L., Long, G., Leggett, H. C., Schmid-Hempel, P., Butlin, R., Martin, S. J. M., & Boots, M. (2016). Deformed wing virus is a recent global epidemic in honeybees driven by Varroa mites. *Science*, *351*(6273), 594–597. doi:10.1126/science.aac9976