



Deposited via The University of Leeds.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/172346/>

Version: Accepted Version

Article:

Tong, X, Compton, SG, Jiao, J et al. (2021) Dual effects of insect fecundity overdispersion on the Wolbachia establishment and the implications for epidemic biocontrol. *Journal of Pest Science*, 94 (4). pp. 1519-1529. ISSN: 1612-4758

<https://doi.org/10.1007/s10340-021-01331-0>

© 2021, The Author(s), under exclusive licence to Springer-Verlag GmbH, DE part of Springer Nature. This is an author produced version of an article published in *Journal of Pest Science*. Uploaded in accordance with the publisher's self-archiving policy.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

1 **Title:** Dual effects of insect fecundity overdispersion on the *Wolbachia* establishment and
2 the implications for epidemic biocontrol

3

4 Xin Tong¹, Stephen G. Compton², Jing Jiao³, Yan Chen⁴, Yuan-Yuan Ding¹, Rong Wang¹,
5 Xiao-Yong Chen^{1,5*}

6

7 1 Zhejiang Tiantong Forest Ecosystem National Observation and Research Station, School
8 of Ecological and Environmental Sciences, East China Normal University, Shanghai
9 200241, China

10 2 School of Biology, University of Leeds, Leeds LS2 9JT, UK

11 3 National Institute for Mathematical and Biological Synthesis, University of Tennessee,
12 Knoxville, TN 37996-3410, USA

13 4 Ecological Security and Protection Key Laboratory of Sichuan Province, Mianyang
14 Normal University, Mianyang, Sichuan 621000, China

15 5 Shanghai Institute of Pollution Control and Ecological Security, Second Zhongshan
16 North Road 1515, Shanghai 200092, China

17

18 * Correspondence:

19 Xiao-Yong Chen

20 School of Ecological and Environmental Sciences,

21 East China Normal University,

22 Shanghai 200241, China

23 Email: xychen@des.ecnu.edu.cn

24 Tel: +86-21-5434-5469

25

26 **Abstract**

27 The utilization of the most prevalent endosymbionts *Wolbachia* spp. to tackle insect-borne
28 viral diseases is growing rapidly. Understanding how and how often *Wolbachia* establish
29 in a local population is fundamental to replacement releases but remains unclear. Previous
30 models make the prediction of poor performance of *Wolbachia* at low frequencies that
31 contradicts the natural ubiquity of those endosymbionts, and the prediction of almost
32 certain fixation of *Wolbachia* at high frequencies that cannot explain the large fluctuations
33 and collapses of infection in field releases. Here, we investigated whether those paradoxes
34 can be reconciled by the stochasticity originating from fecundity overdispersion within
35 host insects. We first reanalyzed published datasets and showed that fecundity was mostly
36 overdispersed in insects. To understand the effects of host fecundity variation on *Wolbachia*
37 establishment, we further constructed a model accounting for cytoplasmic incompatibility
38 and fecundity cost on infected hosts. Based on the empirical results of fecundity
39 overdispersion, the model predicted not only a biologically relevant probability for
40 *Wolbachia* to establish from a single infection, but also a large uncertainty of fixation at
41 high frequencies. These findings will enable a better understanding of endosymbiont-insect
42 dynamics and help design sustainable strategies to control arboviral diseases.

43 **Keywords:** arbovirus; insect endosymbiont; bistable dynamics; stochastic process;
44 negative binomial distribution

45 **Key message**

- 46 ● *Wolbachia* has been widely used to control arboviruses, but how fecundity variation
47 of the vector impacts *Wolbachia* establishment remains unknown.
- 48 ● Fecundity overdispersion was observed in most studied insects, and it may help
49 *Wolbachia* establish from low frequencies but reduce the certainty of fixation at high
50 frequencies.
- 51 ● Fecundity variation should be considered in *Wolbachia*-based vector replacement
52 strategies, and more transduced individuals may need to be released across a longer
53 period than is currently used.

54 **Introduction**

55 Ubiquitous arthropod-borne viruses (arboviruses) have been posing threats to human
56 health for a long time. The pandemic of dengue virus infection has spread to five continents
57 at an unprecedentedly high rate of 390 million cases per year, placing over 3 billion people
58 at risk of the disease (Bhatt et al. 2013; Brady and Hay 2020). Since the first noteworthy
59 epidemic on Yap Island in Micronesia in 2007, Zika virus has caused massive outbreaks
60 throughout South America, Central America, and the Caribbean (Cugola et al. 2016; Fauci
61 and Morens 2016). Besides the developments of effective vaccines and therapeutics against
62 pathogenic arboviruses, control of their vector populations also plays a critical role in
63 epidemic prevention (Ritchie et al. 2018). However, suppressing the vectors through
64 chemical insecticides is challenged by the evolution of resistance (Moyes et al. 2017) and
65 criticism on the damages to ecosystems caused by the chemicals (Pance 2018). Recently,
66 more effective, natural, and self-sustaining biocontrol strategies using endosymbionts have
67 been proposed and developed (Dorigatti et al. 2018; Ghosh et al. 2018; Ross et al. 2019).

68 *Wolbachia* spp. are probably the most abundant endosymbiotic intracellular bacteria
69 infecting more than half of the million-plus species of insects (Hilgenboecker et al. 2008;
70 Zug et al. 2012). Some *Wolbachia* strains have been recognized to effectively inhibit the
71 proliferation and transmission of various RNA arboviruses in their host insects (Hedges et
72 al. 2008; Teixeira et al. 2008), probably through competition over resources and innate
73 immune priming (Terradas and McGraw 2017). However, *Wolbachia* do not naturally
74 occur in some arboviral vectors including the primary vector of Zika, dengue, malaria, and

75 chikungunya (i.e. the *Aedes aegypti* mosquito). A promising avenue for tackling this issue
76 is release of transinfected vectors, which aims at population replacement with virus-
77 blocking *Wolbachia*. So far, introduction of wMel *Wolbachia* strains from *Drosophila*
78 *melanogaster* into *A. aegypti* is the leading transinfection mode, with operational releases
79 in ten countries by the World Mosquito Program (Ritchie et al. 2018). These wMel-releases
80 have resulted in a dramatic reduction (up to 97%) of dengue incidence in the project sites
81 where *Wolbachia* have established at high frequency, in contrast to only a moderate
82 reduction (c. 50%) in hot areas such as Brazil (<https://www.worldmosquitoprogram.org/>).
83 In light of large reduction in invasiveness and virus-blocking capacities for wMel at high
84 temperatures in contrast to wAlbB from *A. albopictus* which is much less susceptible to
85 similar temperatures (Ant et al. 2018; Ross et al. 2017), wAlbB may be well suited for
86 population replacement in hot tropical environments. Recently, *A. aegypti* mosquitoes
87 carrying wAlbB were released at six sites in Kuala Lumpur, Malaysia (Nazni et al. 2019).
88 The strain has been successfully established and maintained at high frequency at some sites,
89 but large fluctuations of *Wolbachia* frequency were also observed (Nazni et al. 2019).

90 A key driver for *Wolbachia* replacement is the induction of cytoplasmic incompatibility
91 (CI), which elevates the mortality of embryos of matings between infected males and
92 uninfected females or females carrying an incompatible *Wolbachia* strain (Hoffmann and
93 Turelli 1997; Laven 1956). Because of maternal transmission of *Wolbachia*, CI provides
94 infected females with a frequency-dependent fitness advantage (Caspari and Watson 1959).
95 Successful establishment of *Wolbachia* then depends on CI outweighing possible fitness

96 cost on infected hosts and outweighing incomplete maternal transmission of infection
97 (Hancock et al. 2011; Turelli 1994). This creates bistable frequency dynamics under which
98 the infection frequency must exceed a threshold for *Wolbachia* to spread rather than to be
99 lost from a population (Caspari and Watson 1959). Other dynamics, such as Fisherian
100 dynamics under which *Wolbachia* will always spread throughout the host populations even
101 with very low initial numbers in the absence of CI (Barton and Turelli 2011), are seldom
102 reported or utilized in arbovirus control (but see Kriesner et al. 2013).

103 However, large fluctuations in infection frequency and thereby obstructions of
104 *Wolbachia* invasion confronting field replacement releases are beyond the prediction of the
105 model. In the *A. aegypti* population of Nogotirto, Indonesia, *w*Mel frequency was raised to
106 more than 80% at the end of field release period, but then oscillated strongly between 50%
107 and 100% (Tantowijoyo et al. 2020). Collapse of *w*Mel introduction has also been observed
108 in Westcourt, Australia (Schmidt et al. 2017) and Rio de Janeiro, Brazil (Garcia et al. 2019).
109 Following the releases of *w*AlbB-carrying *A. aegypti* in Malaysia, the *Wolbachia* frequency
110 once exceeded 95% but subsequently fluctuated and even decreased to 20% at two of four
111 primary intervention sites (Nazni et al. 2019). Temperature susceptibility of *Wolbachia*
112 strain or lack of insecticide resistance in released mosquitoes may account for some
113 unavailing releases (Ant et al. 2018; Garcia et al. 2019), but was proved to have minor
114 effect in some other cases (e.g. Nazni et al. 2019).

115 An alternative and probably more general factor that underlies large fluctuations and
116 thereby collapse of *Wolbachia* introduction is stochastic processes (Engelstadter and

117 Telschow 2009). Previous drift models showed weak impacts of stochasticity on *Wolbachia*
118 dynamics in large host populations, leading to a conclusion that employment of *Wolbachia*
119 as a driving element in pest control normally does not need to consider stochastic effects
120 (Egas et al. 2002; Jansen et al. 2008). However, those models invoked the population
121 genetic parameter ‘effective population size’, i.e. the size of an idealized panmictic
122 population that experiences the same strength of genetic drift as the actual population
123 (Fisher 1930; Wright 1931). This parameter facilitates modelling but can hardly assist
124 *Wolbachia*-based epidemic management, because effective population size is usually
125 unknown for most vector populations and is difficult to estimate accurately (Wang 2016).
126 In contrast, more variation in fecundity than expected by the Poisson distribution (termed
127 ‘overdispersion’), the latter assumed in the Wright–Fisher idealized population (Kimura
128 and Crow 1963), has been observed in many insect species including mosquitoes
129 (Blackmore and Lord 2000; Ferguson et al. 2003; Vezilier et al. 2012). It should be
130 expected that such overdispersion generates more stochasticity to the invasion dynamics
131 of *Wolbachia*, and importantly, that the degree of the overdispersion can be easily estimated
132 in the laboratory or in the field. Overdispersion may also provide an explanation for the
133 paradox between the model prediction of poor performance of *Wolbachia* in a novel host
134 from few infections and the reality that *Wolbachia* have successfully infected millions of
135 arthropod species (Fenton et al. 2011). Nevertheless, fecundity overdispersion has rarely
136 been evaluated empirically in insect populations, nor is it understood how fecundity
137 overdispersion impacts the fates of *Wolbachia* in a local host population.

138 Here we present evidence of fecundity overdispersion in insects through reanalyzing
139 empirical datasets, and construct a general *Wolbachia* frequency-dynamic model explicitly
140 considering host fecundity variation. Based on the empirical estimates of overdispersion,
141 we performed a general analysis using the model. We then further used the model to
142 estimate the number of infected vectors required for successful population replacement, to
143 offer some operational suggestions for optimum release strategies in *Wolbachia*-based
144 biocontrol. Additionally, we also explore how and how often *Wolbachia* succeed to invade
145 a novel host population starting from a single infection, which may provide mechanistic
146 insights into the ubiquity of those endosymbionts.

147

148 **Materials and methods**

149 **Literature search**

150 We conducted a literature search using “TI=(fecundity) AND TS=(insect*)” on the ISI
151 Web of Knowledge database (<http://apps.webofknowledge.com>) in April 2020 to identify
152 experimental data of insect fecundity, yielding a total of 1914 records. We also searched
153 for the fecundity of *A. aegypti* using “TS=(*Aedes aegypti* AND fecundity)”, yielding 672
154 records. We then screened these records according to the following criteria: (i) realized
155 fecundity (not potential fecundity) was measured, (ii) insect fecundity was counted at the
156 individual level, and (iii) there was at least one group of studied insects free of the
157 experimental treatments that are unlikely to occur in natural conditions (e.g., pesticides and
158 RNA interference). After screening, we retained 56 studies for estimation of fecundity

159 dispersion (Appendix S1, Supporting Information).

160

161 **Estimation of fecundity dispersion**

162 For each species examined in each retained study, we calculated the sample size (n),
163 the mean (\bar{x}) and variance (S^2) of fecundity from the deposited data. If original data were
164 not available, these statistics were extracted from main texts or graphs only concerning the
165 insect individuals that met the third criterion. When multiple groups were needed to be
166 combined together (the conditions could occur in the same population, e.g. treatments with
167 different hosts) but the statistics were reported separately for those groups, the total
168 statistics were calculated as $\bar{x} = \sum n_i \bar{x}_i / \sum n_i$ and $S^2 = \sum n_i (S_i^2 + \bar{x}_i^2) / \sum n_i -$
169 $(\sum n_i \bar{x}_i / \sum n_i)^2$ (see Appendix S2). In the cases where only the ranges of fecundity were
170 reported for each group, we randomly sampled n_i values from the corresponding uniform
171 distribution. We then pooled all groups together and calculated the summary statistics
172 based on 10,000 simulations for each species. The Kolmogorov–Smirnov test was used to
173 examine whether the fecundity data were Poisson distributed in each species. If not,
174 overdispersion parameter θ was estimated by $\theta = \bar{x}^2 / (S^2 - \bar{x})$. Zero inflation is a source
175 of overdispersion (Linden and Mantyniemi 2011), but zeros might have been eliminated in
176 data analyses, leading to an underestimation of overdispersion. Hence, we recorded
177 whether zero values were included in each dataset.

178

179 **The model of *Wolbachia* dynamics**

180 We construct a general dynamic model of infection frequency to describe how host
181 fecundity variation together with CI and infection cost impact the fate of *Wolbachia* in a
182 host population. We focus on CI because it is the most frequently found *Wolbachia*-induced
183 reproductive effect (Werren et al. 2008) and most relevant to *Wolbachia* invasion for pest
184 management (Ritchie et al. 2018).

185 We denote the fecundity of the i th infected female and that of the j th uninfected female
186 using $F_{I(i)}$ and $F_{U(j)}$ (both can be zero), which have expected values of λ_1 and λ_2 , respectively.
187 The fecundity cost due to *Wolbachia* parasitism is thus given by $s_f = 1 - \lambda_1/\lambda_2$. We let $H <$
188 1 represent the hatch rate from a CI cross relative to other crosses, and let $\mu \leq 1$ denote the
189 probability for an infected female to transmit *Wolbachia* to its eggs. Thus, $s_h = 1 - H$
190 quantifies the intensity of CI, and $1 - \mu$ quantifies imperfect maternal transmission. We
191 assume discrete generations of the host population, but generation overlap and age structure
192 may be incorporated into our model like Turelli (2010) and Hancock et al. (2011). Panmixia
193 is assumed for the host population, and more realistic nonrandom mating may be reconciled
194 by partitioning the population into several panmictic subpopulations linked via gene flow.

195 The population dynamics of *Wolbachia* can be modelled by tracking changes in the
196 frequency of infected hosts across generations. If the frequency of hosts being infected at
197 generation t is p_t , and the total number of reproductive females within the population is N ,
198 the numbers of crosses are then expected to be Np_t^2 , $Np_t(1-p_t)$, $Np_t(1-p_t)$, and $N(1-p_t)^2$, for
199 IF \times IM, IF \times UM, UF \times IM, and UF \times UM, respectively (I: infected, U: uninfected; F:
200 female, M: male). Multiplying them by the corresponding fecundity and hatch rate, we

201 obtain the recursion equation

$$202 \quad p_{t+1} = \frac{\mu \sum_{i=1}^{Np_t} F_{I(i)}}{\sum_{i=1}^{Np_t} F_{I(i)} + \sum_{j=1}^{N[1-(1+s_h)p_t+s_h p_t^2]} F_{U(j)}} \quad (\text{eqn 1})$$

203 Stochastic deviation of the numbers of crosses from the expectations may exist due to finite
 204 population size, but we argue that the variation can be regarded as a source of dispersion
 205 in fecundity (F_I and F_U). Therefore, equation (1) holds in such cases. For investigating the
 206 role of host fecundity variation in the dynamics of *Wolbachia*, we characterize F_I and F_U
 207 in the following three cases.

208 *Case 1: No variation of fecundity*

209 We first assume constant fecundity, that is, $F_I = \lambda_1$ and $F_U = \lambda_2$. Then, equation (1)
 210 reduces to

$$211 \quad p_{t+1} = \frac{(1-s_f)\mu}{1+s_h p_t^2 - (s_f+s_h)p_t} \cdot p_t \quad (\text{eqn 2})$$

212 and yields three equilibria by setting $p_{t+1} = p_t$:

$$213 \quad p = 0, \quad p = \frac{s_f+s_h - \sqrt{(s_f-s_h)^2 - 4s_h(1-\mu)(1-s_f)}}{2s_h}, \quad \text{and} \quad p = \frac{s_f+s_h + \sqrt{(s_f-s_h)^2 - 4s_h(1-\mu)(1-s_f)}}{2s_h}.$$

214 For a simple example, if we assume perfect maternal transmission (i.e., $\mu = 1$), there
 215 will be two stable equilibria ($p = 0$ and $p = 1$) and one unstable equilibrium ($\hat{p} = s_f/s_h$)
 216 for the infection frequency. When the initial frequency (p_0) is above the establishment
 217 threshold \hat{p} , *Wolbachia* will spread throughout the whole population, but when $p_0 < \hat{p}$,
 218 *Wolbachia* will ultimately be lost in this population. Thus, this case corresponds to those
 219 deterministic models that predict bistable dynamics (Barton and Turelli 2011; Caspari and
 220 Watson 1959; Turelli and Barton 2017; Turelli and Hoffmann 1991).

221 *Case 2: Poisson distribution for dispersed fecundity*

222 We use the Poisson distribution to model moderate variation of host fecundity: $F_I \sim$
223 $\text{Poisson}(\lambda_1)$ and $F_U \sim \text{Poisson}(\lambda_2)$, where the expected variances of F_I and F_U equal to their
224 means (λ_1 and λ_2), respectively. This case corresponds to stochastic models that test for the
225 effects of drift (Jansen et al. 2008; Rigaud and Rousset 1996).

226 *Case 3: Negative binomial distribution for overdispersed fecundity*

227 We take the negative binomial distribution to model F_I and F_U to include the
228 overdispersion of host fecundity, because this distribution has a good performance in
229 characterizing overdispersion of biological count data (Linden and Mantyniemi 2011;
230 Warton et al. 2016). Specifically, the probability functions of F_I and F_U are defined by

231
$$f(F_I = k) = \frac{\Gamma(\theta+k)}{k!\Gamma(\theta)} \left(\frac{\lambda_1}{\theta+\lambda_1}\right)^k \left(\frac{\theta}{\theta+\lambda_1}\right)^\theta \quad (\text{eqn 3})$$

232 and

233
$$f(F_U = k) = \frac{\Gamma(\theta+k)}{k!\Gamma(\theta)} \left(\frac{\lambda_2}{\theta+\lambda_2}\right)^k \left(\frac{\theta}{\theta+\lambda_2}\right)^\theta \quad (\text{eqn 4})$$

234 with the variances $\lambda_1 + \lambda_1^2/\theta$ and $\lambda_2 + \lambda_2^2/\theta$, respectively, where $\theta > 0$ is the dispersion
235 parameter with smaller values representing stronger overdispersion. When θ approaches
236 infinity, the distribution converges to the Poisson distribution.

237 To illustrate how variation of host fecundity affects the fates of *Wolbachia*, we perform
238 numerical simulations for a total of 60 scenarios over the three cases, setting four levels of
239 fecundity cost ($s_f = 0, 0.01, 0.1, \text{ and } 0.25$), three levels of host population size ($N = 10^2,$
240 $10^3, \text{ and } 10^4$), and six distributions of fecundity (constant, Poisson, and four negative
241 binomials with $\theta = 0.01, 0.1, 1 \text{ and } 10$ according to the empirical results). Perfect maternal

242 transmission (i.e., $\mu = 1$) and complete CI (i.e., $s_h = 1$) are assumed in all scenarios, which
243 is reasonable for a variety of *Wolbachia* strains in *A. aegypti* (Ant et al. 2018; Hoffmann et
244 al. 2014). For each scenario, we set the initial infection frequency (p_0) from 0.01 to 0.99
245 with an increase of 0.01 each time and then calculated p_1, p_2, \dots using equation (1) until p_i
246 = 0 or 1. In the scenarios with fecundity variation, values of $F_{1(i)}$ and $F_{U(j)}$ are sampled from
247 the Poisson distribution or using equations (3) and (4). One thousand simulations are run
248 for each p_0 of each scenario to determine the probability of *Wolbachia* fixation.

249

250 **Applications of the model**

251 We used the model to address two specific issues. First, we estimated the number of
252 infected *A. aegypti* mosquitoes that need to be released in order to ensure a high probability
253 (say, ≥ 0.95) for successful *Wolbachia* invasion, when there is overdispersion in host
254 fecundity. The fecundity cost on *Wolbachia*-infected *A. aegypti* was estimated at *c.* 20%
255 for wMel infection (Hoffmann et al. 2011) and 10%–15% for wAlbB infection (Axford et
256 al. 2016; Xi et al. 2005). We thus assumed fecundity cost at $s_f = 0.15$. The dispersion
257 parameter θ was set to vary over the range 0.01–10, according to the empirical estimates.
258 The number of reproductive female mosquitoes N was set at 10^2 , 10^3 and 10^4 . For
259 comparison, simulations with the same settings except for θ were also performed in cases
260 where host fecundity is fixed or Poisson distributed.

261 Second, the model was used to estimate the probability of *Wolbachia*'s fixation
262 following the introduction of a single infected female into a population (i.e. $p_0 = 1/N$)

263 through interspecific horizontal transfers. For comparison, we used the same settings of
264 fecundity cost as Jansen et al. (2008). Given the empirical results of fecundity
265 overdispersion in insects, we considered four plausible scenarios of overdispersion, i.e. θ
266 = 10, 1, 0.1, and 0.01, and use Poisson-distributed fecundity as the control. We ran the
267 model one million times for each combination of parameters to get the probability of
268 fixation of *Wolbachia*.

269

270 **Results**

271 **Fecundity overdispersion**

272 We obtained a total of 56 articles that met the three criteria, involving 47 species and
273 79 datasets. Only one of them (grain aphid *Sitobion avenae*) showed a Poisson-type
274 distribution of fecundity, with the variance close to the mean (23.74 vs. 26.09, $P = 0.58$).
275 Overdispersion was found in all other cases, with estimates of overdispersion parameter θ
276 0.01–20.29 (median: 2.6). The largest overdispersion ($\theta = 0.01$) was found in the eusocial
277 red ant *Myrmica rubra*. Besides *S. avenae*, 57 datasets did not include zero values, which
278 produced significantly larger θ (i.e., less overdispersion) than the 21 datasets with zeros
279 ($5.04 \pm \text{SE } 0.58$ vs. $0.80 \pm \text{SE } 0.11$, Mann–Whitney $U = 1121$, $P < 0.001$; Fig. 1). For the
280 same species, parameter θ was overestimated by approximately one order of magnitude
281 (median: 4.08-fold) when zero values were overlooked (Fig. 1). Summary statistics of all
282 studies are provided in Table S1.

283 Among the datasets involving *A. aegypti* ($n = 14$), six studies reported zero values and

284 displayed substantial fecundity overdispersion, with θ ranging 0.55–1.57 (median 1.05).
285 The remaining eight datasets that did not include zero values showed much weaker
286 overdispersion, where θ varied between 1.97 and 7.39 (median 4.50). When zero values
287 were deliberately excluded from the with-zero datasets, the increases in the estimate of θ
288 were large in two of three cases (Fig. 1).

289

290 ***Wolbachia* fixation from different initial frequencies**

291 The fixation probability displays a step function of initial infection frequency (p_0) if
292 assuming no variation for host fecundity (case 1), but turns to a sigmoid function when
293 fecundity is Poisson-distributed (case 2) or overdispersed (case 3). Compared to Poisson-
294 distributed fecundity, overdispersed fecundity produces smoother curves for the fixation
295 probability function (Fig. 2). More generally, when the overdispersion in fecundity become
296 larger (with a smaller θ), the model provides smoother curves for the fixation probability
297 function at all levels of fecundity cost (Fig. 2).

298 When p_0 is smaller than the threshold (\hat{p}) predicted by the deterministic model, the
299 model predicts non-zero fixation probabilities when there are some variations in fecundity,
300 and these probabilities generally increase with larger extent of fecundity dispersion (Fig.
301 2). For example, a *Wolbachia* strain causing fecundity cost of 25% is always unable to fix
302 itself in a host population of 1000 reproductive females, when the initial infection
303 frequency is 0.17 and host fecundity is Poisson distributed (Fig. 2f). In contrast, the strain
304 has a 9.2% chance to achieve fixation if host fecundity shows a negative binomial

305 distribution with $\theta = 0.1$. When $p_0 > \hat{p}$, however, overdispersion can introduce larger
306 variation to *Wolbachia* fixation, and the uncertainty of fixation increases with stronger
307 overdispersion (e.g., $p_0 > 0.25$ in Fig. 2f). This trend is extremely strong when population
308 size is relatively small (e.g., comparing Fig. 2c and f).

309

310 **Application 1: replacement releases of *Wolbachia*-infected vectors**

311 In the vector population replacement with *Wolbachia*, fecundity variation significantly
312 elevates the number of infected vectors that should be released to ensure the successful
313 invasion of *Wolbachia* (Fig. 3). For a vector population of 1000 reproductive females, 27%
314 more *Wolbachia*-carrying vectors are required than predicted by the deterministic model
315 when accounting for Poisson-distributed fecundity. This proportion increases to 33%, 40%,
316 80% and 220% when fecundity is overdispersed with θ of 10, 1, 0.1 and 0.01, respectively.
317 The strength of such effect of fecundity variation depends negatively on population size.
318 The required initial infection frequency increases at an astonishing rate in a population of
319 100 reproductive females when fecundity variation becomes larger, whereas the impacts of
320 overdispersion are much weaker in a very large population (e.g. 10000 reproductive
321 females) (Fig. 3). Nevertheless, there is still a substantial effect that need to be considered
322 in such large populations if fecundity overdispersion is of the order of $\theta = 0.1$ (Fig. 3).

323 When regarding the primary vector of Zika and dengue fever, *A. aegypti*, based on the
324 empirical estimates of fecundity overdispersion of $\theta = 0.55$ – 1.57 (Fig. 1), our model
325 predicts that the numbers of released mosquitoes into a population of 100, 1000 and 10000

326 reproductive females need to exceed the expectations from the deterministic model by
327 107%–130%, 33%–40%, and 13%, and exceed those from the stochastic model by 11%–
328 23%, 5%–11%, and 0%, respectively (Fig. 3).

329

330 **Application 2: spread of *Wolbachia* from a single infection**

331 When assuming Poisson-distributed host fecundity, the fixation probability declines
332 with population size in an approximately linear manner on the log-log plot if the *Wolbachia*
333 strains are neutral to their hosts (Fig. 4a). When population size is small, the fixation
334 probability of a weakly deleterious *Wolbachia* strain is close to the neutral one, but the
335 discrepancy enlarges rapidly as the deleterious effect of *Wolbachia* and/or population size
336 increases (Fig. 3a). Note that a strain with cost $s_f = 0.125$ is still unable to establish itself
337 in any population of $N > 600$ following one million events of lateral introduction of a single
338 infection.

339 Overdispersion of host fecundity increases the probability of *Wolbachia* spreading to
340 fixation from a single infection in a host population, and this effect becomes stronger when
341 population size, the deleterious effect of *Wolbachia*, and the magnitude of overdispersion
342 increase (Fig. 3 b–d). In contrast to the Poisson scenario, a strain with cost $s_f = 0.125$
343 achieves fixation in a host population of $N = 631$ every 550 events of introducing a single
344 infection if host fecundity is overdispersed with $\theta = 0.1$.

345

346 **Discussion**

347 This study provides to our knowledge the first assessment of overdispersion in insect
348 fecundity and its effect on the invasion dynamics of *Wolbachia*. Empirical data present
349 compelling evidence for overdispersion of fecundity in most studied insect species.
350 Furthermore, our model demonstrates that the overdispersion may help CI-inducing
351 *Wolbachia* spread in novel hosts from few infections, but can also undermine vector
352 population replacement with *Wolbachia* in epidemic management.

353 Our analysis may provide an underestimate for fecundity overdispersion in many insect
354 species due to several reasons. First, the conspecific insects used here to estimate fecundity
355 variation were reared under almost the same condition in each dataset. However,
356 environmental heterogeneity, variation in the availability and quality of food and mates,
357 and other biotic factors may augment the overdispersion of fecundity in field populations
358 (Awmack and Leather 2002; Borer et al. 2009; Reigada et al. 2018; Zanchi et al. 2012).
359 Second, zero-inflation is an important source of overdispersion (Linden and Mantyniemi
360 2011), as shown by the large overdispersion of the eusocial species *Myrmica rubra* ($\theta =$
361 0.01). Most studies reviewed here were not designed to test the variation of fecundity, and
362 therefore some oviposition failures might be treated as noise and excluded artificially.
363 However, null fecundity has a close relevance to the invasion of *Wolbachia*, because it may
364 directly lead to the loss of *Wolbachia*. Additionally, copious oviposition sites were supplied
365 for each adult in those studies, whereas competition for oviposition sites may occur in field
366 populations of some species, resulting in lower or even null fecundity of some adults. This
367 is likely the case in two populations of *A. aegypti* with *wAlbB*-releases in Malaysia, where

368 the population sizes decreased considerably following the cessation of releases (Nazni et
369 al. 2019).

370 Consistent with the results of previous stochastic models (Egas et al. 2002; Jansen et
371 al. 2008), our model suggests it is usually difficult for a deleterious *Wolbachia* strain to
372 spread from few initial infections if host fecundity is Poisson distributed. Repeated
373 *Wolbachia* transfers can compensate for the extremely low fixation probability of a single
374 transfer event (Jansen et al. 2008), but in this situation it is unclear whether the waiting
375 time for fixation is biologically relevant. In our study, the estimated probabilities of
376 *Wolbachia* reaching fixation from a single infection in host populations of overdispersed
377 fecundity appear to relax the assumptions of Jansen et al. (2008) on transfer rate and
378 waiting time, and may reconcile the contradictions among occasional and probably rare
379 interspecific transfer events (Turelli et al. 2018), bistable population dynamics (Barton and
380 Turelli 2011), and the remarkable prevalence of *Wolbachia* (Werren et al. 2008).

381 The uncertainty in the fixation of *Wolbachia* caused by overdispersion of host fecundity
382 (see Figs. 2 and 3) may to some extent explain the large fluctuations of *Wolbachia*
383 frequency in some *A. aegypti* populations after replacement releases (Nazni et al. 2019;
384 Schmidt et al. 2017; Tantowijoyo et al. 2020). Especially for the releases of *A. aegypti* in
385 Malaysia, lack of *wAlbB* invasion was found in low-density sites where oviposition sites
386 might be rare (Nazni et al. 2019). This phenomenon is consistent with the expectations of
387 large overdispersion of fecundity. Although we illustrate a special case of $s_f = 0.15$, the
388 need for increasing released individuals is prevalent across diverse fecundity costs of

389 *Wolbachia* infection and becomes even more critical when the cost is smaller (see Fig. 2).
390 In light of great efforts being made to search for *Wolbachia* strains of low fecundity costs
391 (Ant et al. 2018; Pance 2018), the significance of considering fecundity overdispersion in
392 successful vector control is likely to increase further.

393 Nevertheless, the effects of fecundity overdispersion may be counterbalanced by other
394 factors that have not been included in the model. An important factor particularly for *A.*
395 *aegypti* is larval density-dependent competition (Hancock et al. 2016a). This density effect
396 is likely to weaken the overdispersion effects, due to the tradeoff between adult fecundity
397 and larval fitness. Yet, the outcomes of density dependence for *Wolbachia*-based biocontrol
398 strategies are very similar to those of overdispersion, i.e. greater numbers of released
399 mosquitoes and longer time of *Wolbachia* establishment following releases (Hancock et al.
400 2016a; Hancock et al. 2016b). While increased mortality due to *Wolbachia* infection,
401 imperfect maternal transmission (e.g. at high temperatures), or occurrence of adverse
402 conditions, may augment the effects of overdispersion (Jansen et al. 2008).

403 Our model focuses on CI-inducing *Wolbachia* strains especially *wMel* and *wAlbB*.
404 However, the *wAu* strain which does not induce CI shows more efficient virus blocking
405 and greater temperature stability than the two strains (Ant et al. 2018). Hence, a
406 superinfection *wAu-wAlbB* was created to combine strong viral inhibition and CI, and has
407 been proposed as a novel biocontrol agent (Ant et al. 2018). Intriguingly, our model can
408 also apply for the superinfection, but if *wAu* and *wAlbB* decoupled over time in the field,
409 only the dynamics of *wAlbB* would be described by our model.

410 Our model assumes a panmictic population, but mating is often nonrandom in the field
411 populations, especially when it routinely takes place at breeding sites before individuals
412 disperse (Macke et al. 2011). After an initial phase of local establishment, *Wolbachia* may
413 spread to other areas in a wave of colonization (Barton and Turelli 2011; Schmidt et al.
414 2017) or via stepping stone subpopulations (Engelstadter and Telschow 2009). In both
415 cases, spatial spread can be slowed or even stopped if the host density is much higher in
416 surrounding uninfected areas, because there are insufficient migrants transporting
417 *Wolbachia*. These areas are analogous to the ‘tension zones’ where transitions occur
418 between alternative genetic equilibria. Local fluctuations in population density and
419 dispersal rate can drive development and movement of these tension zones (Barton 1979;
420 Barton and Hewitt 1989). Nonetheless, the increased probabilities of fixation caused by
421 overdispersion in host fecundity should help *Wolbachia* to pass through such tension zones
422 via few migrants.

423 In conclusion, fecundity overdispersion is ubiquitous in insect populations, placing
424 large stochasticity on the dynamics of *Wolbachia*. The significance of this stochasticity has
425 been underestimated in both explaining the pandemic distribution of *Wolbachia* and
426 formulating strategies for sustainable biocontrol of insect-borne diseases with *Wolbachia*.
427 Our study address that efforts should be made to understand the dispersion of fecundity in
428 the target vector populations before decision on the nature of the *Wolbachia* releases, and
429 also that the stochasticity brought by fecundity overdispersion greatly contributes to the
430 local establishment and spatial spread of *Wolbachia* after the releases.

431

432 **Funding:** This study was funded by the National Natural Science Foundation of China
433 (31630008, 31270416, 31870356).

434 **Conflict of Interest:** The authors declare that they have no conflict of interest.

435 **Availability of data and material:** Not applicable.

436 **Ethics approval:** Not applicable.

437 **Consent to participate:** Not applicable.

438 **Consent for publication:** Not applicable.

439 **Code availability:** The R code is attached as a supplementary file.

440 **Author Contribution Statement:** XYC and XT conceived and designed research. XT and
441 JJ constructed models. XT, XYC, SGC, YC, YYD, RW and JJ analyzed data. XT wrote the
442 manuscript. All authors read and approved the manuscript.

443

444 **References:**

445 Ant TH, Herd CS, Geoghegan V, Hoffmann AA, Sinkins SP (2018) The *Wolbachia* strain *w*Au provides
446 highly efficient virus transmission blocking in *Aedes aegypti*. PLoS Pathog 14:e1006815.
447 <https://doi.org/10.1371/journal.ppat.1006815>

448 Awmack CS, Leather SR (2002) Host plant quality and fecundity in herbivorous insects. Annu Rev Entomol
449 47:817–844

450 Axford JK, Ross PA, Yeap HL, Callahan AG, Hoffmann AA (2016) Fitness of *w*AlbB *Wolbachia* infection in
451 *Aedes aegypti*: parameter estimates in an outcrossed background and potential for population
452 invasion. Am J Trop Med Hyg 94:507–516. <https://doi.org/10.4269/ajtmh.15-0608>

453 Barton NH (1979) The dynamics of hybrid zones. Heredity 43:341–359

454 Barton NH, Hewitt GM (1989) Adaptation, speciation and hybrid zones. Nature 341:497–503

455 Barton NH, Turelli M (2011) Spatial waves of advance with bistable dynamics: cytoplasmic and genetic
456 analogues of Allee effects. Am Nat 178:E48–E75. <https://doi.org/10.1086/661246>

457 Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, Drake JM, Brownstein JS, Hoen AG,

458 Sankoh O, Myers MF, George DB, Jaenisch T, Wint GRW, Simmons CP, Scott TW, Farrar JJ, Hay
459 SI (2013) The global distribution and burden of dengue. *Nature* 496:504–507.
460 <https://doi.org/10.1038/nature12060>

461 Blackmore MS, Lord CC (2000) The relationship between size and fecundity in *Aedes albopictus*. *J Vector*
462 *Ecol* 25:212–217

463 Borer ET, Adams VT, Engler GA, Adams AL, Schumann CB, Seabloom EW (2009) Aphid fecundity and
464 grassland invasion: invader life history is the key. *Ecol Appl* 19:1187–1196.
465 <https://doi.org/10.1890/08-1205.1>

466 Brady OJ, Hay SI (2020) The global expansion of dengue: How *Aedes aegypti* mosquitoes enabled the first
467 pandemic arbovirus. *Annu Rev Entomol* 65:191–208. [https://doi.org/10.1146/annurev-ento-](https://doi.org/10.1146/annurev-ento-011019-024918)
468 [011019-024918](https://doi.org/10.1146/annurev-ento-011019-024918)

469 Brahma A, Mandal S, Gadagkar R (2018) Emergence of cooperation and division of labor in the primitively
470 eusocial wasp *Ropalidia marginata*. *Proc Natl Acad Sci USA* 115:756–761.
471 <https://doi.org/10.1073/pnas.1714006115>

472 Caspari E, Watson GS (1959) On the evolutionary importance of cytoplasmic sterility in mosquitoes.
473 *Evolution* 13:568–570

474 Cugola FR, Fernandes IR, Russo FB, Freitas BC, Dias JLM, Guimaraes KP, Benazzato C, Almeida N,
475 Pignatari GC, Romero S, Polonio CM, Cunha I, Freitas CL, Brandao WN, Rossato C, Andrade DG,
476 Faria DD, Garcez AT, Buchpiguel CA, Braconi CT, Mendes E, Sall AA, Zanotto PMD, Peron JPS,
477 Muotri AR, Beltrao-Braga PCB (2016) The Brazilian Zika virus strain causes birth defects in
478 experimental models. *Nature* 534:267–271. <https://doi.org/10.1038/nature18296>

479 Dorigatti I, McCormack C, Nedjati-Gilani G, Ferguson NM (2018) Using *Wolbachia* for dengue control:
480 insights from modelling. *Trends Parasitol* 34:102–113. <https://doi.org/10.1016/j.pt.2017.11.002>

481 Egas M, Vala F, Breeuwer JAJ (2002) On the evolution of cytoplasmic incompatibility in haplodiploid species.
482 *Evolution* 56:1101–1109. <https://doi.org/10.1111/j.0014-3820.2002.tb01424.x>

483 Engelstadter J, Telschow A (2009) Cytoplasmic incompatibility and host population structure. *Heredity*
484 103:196–207. <https://doi.org/10.1038/hdy.2009.53>

485 Fauci AS, Morens DM (2016) Zika virus in the Americas – yet another arbovirus threat. *New Engl J Med*
486 374:601–604. <https://doi.org/10.1056/NEJMp1600297>

487 Fenton A, Johnson KN, Brownlie JC, Hurst GDD (2011) Solving the *Wolbachia* paradox: modeling the
488 tripartite interaction between host, *Wolbachia*, and a natural enemy. *Am Nat* 178:333–342.
489 <https://doi.org/10.1086/661247>

490 Ferguson HM, Rivero A, Read AF (2003) The influence of malaria parasite genetic diversity and anaemia on
491 mosquito feeding and fecundity. *Parasitology* 127:9–19.
492 <https://doi.org/10.1017/S0031182003003287>

493 Fisher RA (1930) *The genetical theory of natural selection*. Clarendon Press, Oxford,

494 Garcia GD, Sylvestre G, Aguiar R, da Costa GB, Martins AJ, Lima JBP, Petersen MT, Lourenco-de-Oliveira
495 R, Shadbolt MF, Rasic G, Hoffmann AA, Villela DAM, Dias FBS, Dong Y, O'Neill SL, Moreira LA,
496 Maciel-de-Freitas R (2019) Matching the genetics of released and local *Aedes aegypti* populations
497 is critical to assure *Wolbachia* invasion. *PLoS Negl Trop Dis* 13:e0007023.
498 <https://doi.org/10.1371/journal.pntd.0007023>

499 Ghosh S, Bouvaine S, Richardson SCW, Ghanim M, Maruthi MN (2018) Fitness costs associated with
500 infections of secondary endosymbionts in the cassava whitefly species *Bemisia tabaci*. *J Pest Sci*
501 91:17–28. <https://doi.org/10.1007/s10340-017-0910-8>

502 Hancock PA, Sinkins SP, Godfray HCJ (2011) Population dynamic models of the spread of *Wolbachia*. *Am*
503 *Nat* 177:323–333. <https://doi.org/10.1086/658121>

504 Hancock PA, White VL, Callahan AG, Godfray CHJ, Hoffmann AA, Ritchie SA (2016a) Density-dependent
505 population dynamics in *Aedes aegypti* slow the spread of wMel *Wolbachia*. *J Appl Ecol* 53:785–793.
506 <https://doi.org/10.1111/1365-2664.12620>

507 Hancock PA, White VL, Ritchie SA, Hoffmann AA, Godfray HCJ (2016b) Predicting *Wolbachia* invasion
508 dynamics in *Aedes aegypti* populations using models of density-dependent demographic traits. *BMC*
509 *Biol* 14:96. <https://doi.org/10.1186/s12915-016-0319-5>

510 Hedges LM, Brownlie JC, O'Neill SL, Johnson KN (2008) *Wolbachia* and virus protection in insects. *Science*
511 322:702–702. <https://doi.org/10.1126/science.1162418>

512 Hilgenboecker K, Hammerstein P, Schlattmann P, Telschow A, Werren JH (2008) How many species are
513 infected with *Wolbachia*? – a statistical analysis of current data. *FEMS Microbiol Lett* 281:215–220.
514 <https://doi.org/10.1111/j.1574-6968.2008.01110.x>

515 Hoffmann AA, Iturbe-Ormaetxe I, Callahan AG, Phillips B, Billington K, Axford JK, Montgomery B, Turley
516 AP, O'Neill SL (2014) Stability of the wMel *Wolbachia* infection following invasion into *Aedes*
517 *aegypti* populations. *PLoS Negl Trop Dis* 8:e3115. <https://doi.org/10.1371/journal.pntd.0003115>

518 Hoffmann AA, Montgomery BL, Popovici J, Iturbe-Ormaetxe I, Johnson PH, Muzzi F, Greenfield M, Durkan
519 M, Leong YS, Dong Y, Cook H, Axford J, Callahan AG, Kenny N, Omodei C, McGraw EA, Ryan
520 PA, Ritchie SA, Turelli M, O'Neill SL (2011) Successful establishment of *Wolbachia* in *Aedes*
521 populations to suppress dengue transmission. *Nature* 476:454–457.
522 <https://doi.org/10.1038/nature10356>

523 Hoffmann AA, Turelli M (1997) Cytoplasmic incompatibility in insects. In: O'Neill SL, Hoffmann AA,
524 Werren JH (eds) *Influential passengers: inherited microorganisms and arthropod reproduction*.
525 Oxford University Press, Oxford, pp 42–80

526 Jansen VAA, Turelli M, Godfray HCJ (2008) Stochastic spread of *Wolbachia*. *Proc R Soc B* 275:2769–2776.
527 <https://doi.org/10.1098/rspb.2008.0914>

528 Kimura M, Crow JF (1963) The measurement of effective population number. *Evolution* 17:279–288

529 Kriesner P, Hoffmann AA, Lee SF, Turelli M, Weeks AR (2013) Rapid sequential spread of two *Wolbachia*
530 variants in *Drosophila simulans*. *PLoS Pathog* 9:e1003607.
531 <https://doi.org/10.1371/journal.ppat.1003607>

532 Laven H (1956) Cytoplasmic inheritance in *Culex*. *Nature* 177:141–142. <https://doi.org/10.1038/177141a0>

533 Linden A, Mantyniemi S (2011) Using the negative binomial distribution to model overdispersion in
534 ecological count data. *Ecology* 92:1414–1421. <https://doi.org/10.1890/10-1831.1>

535 Macke E, Magalhaes S, Bach F, Olivieri I (2011) Experimental evolution of reduced sex ratio adjustment
536 under local mate competition. *Science* 334:1127–1129. <https://doi.org/10.1126/science.1212177>

537 Moyes CL, Vontas J, Martins AJ, Ng LC, Koou SY, Dusfour I, Raghavendra K, Pinto J, Corbel V, David JP,
538 Weetman D (2017) Contemporary status of insecticide resistance in the major *Aedes* vectors of
539 arboviruses infecting humans. *PLoS Negl Trop Dis* 11:e0005625.

540 <https://doi.org/10.1371/journal.pntd.0005625>

541 Nazni WA, Hoffmann AA, NoorAfizah A, Cheong YL, Mancini MV, Golding N, Kamarul GMR, Arif MAK,
542 Thohir H, NurSyamimi H, ZatilAqmar MZ, NurRuqqayah M, NorSyazwani A, Faiz A, Irfan FRMN,
543 Rubaaini S, Nuradila N, Nizam NMN, Irwan SM, Endersby-Harshman NM, White VL, Ant TH,
544 Herd CS, Hasnor AH, AbuBakar R, Hapsah DM, Khadijah K, Kamilan D, Lee SC, Paid YM,
545 Fadzilah K, Topek O, Gill BS, Lee HL, Sinkins SP (2019) Establishment of *Wolbachia* strain wAlbB
546 in Malaysian populations of *Aedes aegypti* for dengue control. *Curr Biol* 29:4241–4248.
547 <https://doi.org/10.1016/j.cub.2019.11.007>

548 Pance A (2018) Can *Wolbachia* save the day? *Nat Rev Microbiol* 16:396–396.
549 <https://doi.org/10.1038/s41579-018-0021-4>

550 Reigada C, Moral RD, Demetrio CGB, Parra JRP (2018) Cross-crop effects on larval growth, survivorship
551 and fecundity of *Helicoverpa armigera*. *J Pest Sci* 91:121–131. [https://doi.org/10.1007/s10340-017-](https://doi.org/10.1007/s10340-017-0893-5)
552 [0893-5](https://doi.org/10.1007/s10340-017-0893-5)

553 Rigaud T, Rousset F (1996) What generates the diversity of *Wolbachia*-arthropod interactions? *Biodivers*
554 *Conserv* 5:999–1013.

555 Ritchie SA, van den Hurk AF, Smout MJ, Staunton KM, Hoffmann AA (2018) Mission accomplished? We
556 need a guide to the ‘post release’ world of *Wolbachia* for *Aedes*-borne disease control. *Trends*
557 *Parasitol* 34:217–226. <https://doi.org/10.1016/j.pt.2017.11.011>

558 Ross PA, Turelli M, Hoffmann AA (2019) Evolutionary ecology of *Wolbachia* releases for disease control.
559 *Annu Rev Genet* 53:93–116. <https://doi.org/10.1146/annurev-genet-112618-043609>

560 Ross PA, Wiwatanaratnabutr I, Axford JK, White VL, Endersby-Harshman NM, Hoffmann AA (2017)
561 *Wolbachia* infections in *Aedes aegypti* differ markedly in their response to cyclical heat stress. *PLoS*
562 *Pathog* 13:e1006006. <https://doi.org/10.1371/journal.ppat.1006006>

563 Schmidt TL, Barton NH, Rasic G, Turley AP, Montgomery BL, Iturbe-Ormaetxe I, Cook PE, Ryan PA,
564 Ritchie SA, Hoffmann AA, O'Neill SL, Turelli M (2017) Local introduction and heterogeneous
565 spatial spread of dengue-suppressing *Wolbachia* through an urban population of *Aedes aegypti*.
566 *PLoS Biol* 15:e2001894. <https://doi.org/10.1371/journal.pbio.2001894>

567 Smith AA, Liebig J (2017) The evolution of cuticular fertility signals in eusocial insects. *Curr Opin Insect*
568 *Sci* 22:79–84. <https://doi.org/10.1016/j.cois.2017.05.017>

569 Stern DL, Foster WA (1996) The evolution of soldiers in aphids. *Biol Rev* 71:27–79.
570 <https://doi.org/10.1111/j.1469-185X.1996.tb00741.x>

571 Tantowijoyo W, Andari B, Arguni E, Budiwati N, Nurhayati I, Fitriana I, Ernesia I, Daniwijaya EW, Supriyati
572 E, Yudianta DH, Victorious M, Wardana DS, Ardiansyah H, Ahmad RA, Ryan PA, Simmons CP,
573 Hoffmann AA, Rances E, Turley AP, Johnson P, Utarini A, O'Neill SL (2020) Stable establishment
574 of wMel *Wolbachia* in *Aedes aegypti* populations in Yogyakarta, Indonesia. *PLoS Negl Trop Dis*
575 14:e0008157. <https://doi.org/10.1371/journal.pntd.0008157>

576 Teixeira L, Ferreira A, Ashburner M (2008) The bacterial symbiont *Wolbachia* induces resistance to RNA
577 viral infections in *Drosophila melanogaster*. *PLoS Biol* 6:2753–2763.
578 <https://doi.org/10.1371/journal.pbio.1000002>

579 Terradas G, McGraw EA (2017) *Wolbachia*-mediated virus blocking in the mosquito vector *Aedes aegypti*.
580 *Curr Opin Insect Sci* 22:37–44. <https://doi.org/10.1016/j.cois.2017.05.005>

581 Turelli M (1994) Evolution of incompatibility-inducing microbes and their hosts. *Evolution* 48:1500–1513
582 Turelli M (2010) Cytoplasmic incompatibility in populations with overlapping generations. *Evolution*
583 64:232–241. <https://doi.org/10.1111/j.1558-5646.2009.00822.x>
584 Turelli M, Barton NH (2017) Deploying dengue-suppressing *Wolbachia*: robust models predict slow but
585 effective spatial spread in *Aedes aegypti*. *Theor Popul Biol* 115:45–60.
586 <https://doi.org/10.1016/j.tpb.2017.03.003>
587 Turelli M, Cooper BS, Richardson KM, Ginsberg PS, Peckenpaugh B, Antelope CX, Kim KJ, May MR,
588 Abrieux A, Wilson DA, Bronski MJ, Moore BR, Gao JJ, Eisen MB, Chiu JC, Conner WR, Hoffmann
589 AA (2018) Rapid global spread of wRi-like *Wolbachia* across multiple *Drosophila*. *Curr Biol*
590 28:963–971. <https://doi.org/10.1016/j.cub.2018.02.015>
591 Turelli M, Hoffmann AA (1991) Rapid spread of an inherited incompatibility factor in California *Drosophila*.
592 *Nature* 353:440–442
593 Vezilier J, Nicot A, Gandon S, Rivero A (2012) Plasmodium infection decreases fecundity and increases
594 survival of mosquitoes. *Proc R Soc B* 279:4033–4041. <https://doi.org/10.1098/rspb.2012.1394>
595 Wang JL (2016) A comparison of single-sample estimators of effective population sizes from genetic marker
596 data. *Mol Ecol* 25:4692–4711. <https://doi.org/10.1111/mec.13725>
597 Warton DI, Lyons M, Stoklosa J, Ives AR (2016) Three points to consider when choosing a LM or GLM test
598 for count data. *Methods Ecol Evol* 7:882–890. <https://doi.org/10.1111/2041-210X.12552>
599 Werren JH, Baldo L, Clark ME (2008) *Wolbachia*: master manipulators of invertebrate biology. *Nat Rev*
600 *Microbiol* 6:741–751. <https://doi.org/10.1038/nrmicro1969>
601 Wright S (1931) Evolution in Mendelian populations. *Genetics* 16:97–159
602 Xi ZY, Khoo CCH, Dobson SL (2005) *Wolbachia* establishment and invasion in an *Aedes aegypti* laboratory
603 population. *Science* 310:326–328. <https://doi.org/10.1126/science.1117607>
604 Zanchi C, Troussard JP, Moreau J, Moret Y (2012) Relationship between maternal transfer of immunity and
605 mother fecundity in an insect. *Proc R Soc B* 279:3223–3230.
606 <https://doi.org/10.1098/rspb.2012.0493>
607 Zug R, Koehncke A, Hammerstein P (2012) Epidemiology in evolutionary time: the case of *Wolbachia*
608 horizontal transmission between arthropod host species. *J Evol Biol* 25:2149–2160.
609 <https://doi.org/10.1111/j.1420-9101.2012.02601.x>

Figure captions

610

611 **Fig. 1** Empirical estimates of overdispersion in realized fecundity for 47 insect species.

612 Smaller values of θ represent stronger overdispersion. The estimate for *Sitobion*

613 *avenae* is not given, because the species showed Poisson-distributed fecundity. Each

614 estimate is derived from one study except in *Aedes aegypti* and *A. albopictus*, and the

615 numbers of studies used for the two species are shown. The difference of estimates

616 between with- and without-zero datasets for the same species is denoted by solid line

617 when the same study is used in both cases, or by dash line when using different studies.

618 All estimates from with- and without-zero datasets, respectively, are summarized by

619 boxplots. Insert shows the estimates for *A. aegypti* from each study.

620 **Fig. 2** The probability of local fixation of *Wolbachia* as a function of initial infection

621 frequency, with varying levels of parasitism cost (s_f), host population size (N), and

622 host fecundity variation. The variation of fecundity increases from no dispersion

623 (black lines), dispersion (green lines), to overdispersion (purple, blue, yellow and red

624 lines). For each p_0 under each parameter setting, the model is conducted 1000 times

625 to estimate the fixation probability. Scenarios with $s_f = 0$ are very similar to those with

626 $s_f = 0.01$, and thus not shown here.

627 **Fig. 3** The initial frequencies for ensuring a probability of 95% for successful establishment

628 of *Wolbachia* in relation to host fecundity overdispersion. Smaller θ values represent

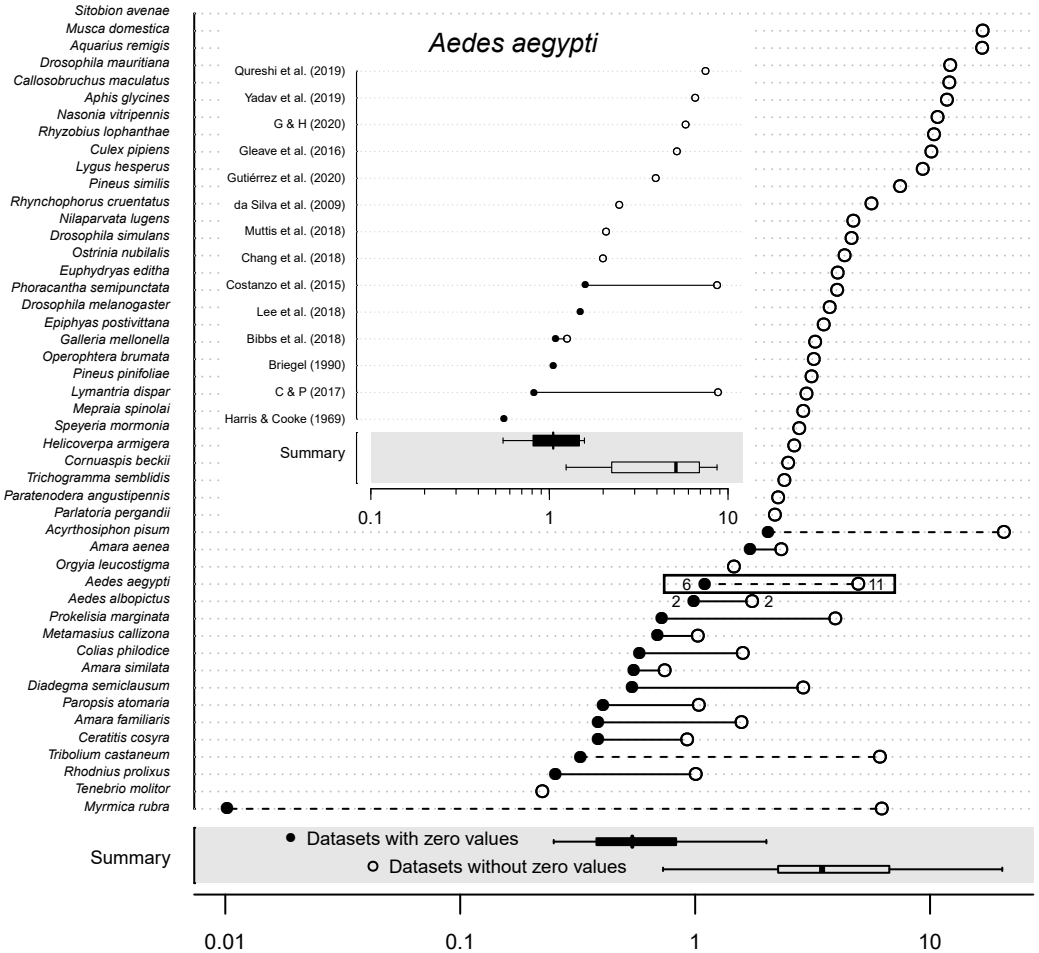
629 larger overdispersion. Three population sizes (N) are considered, and we assume $s_f =$

630 0.15 , $s_h = 1$, and $\mu = 1$. The predictions from the deterministic and stochastic models

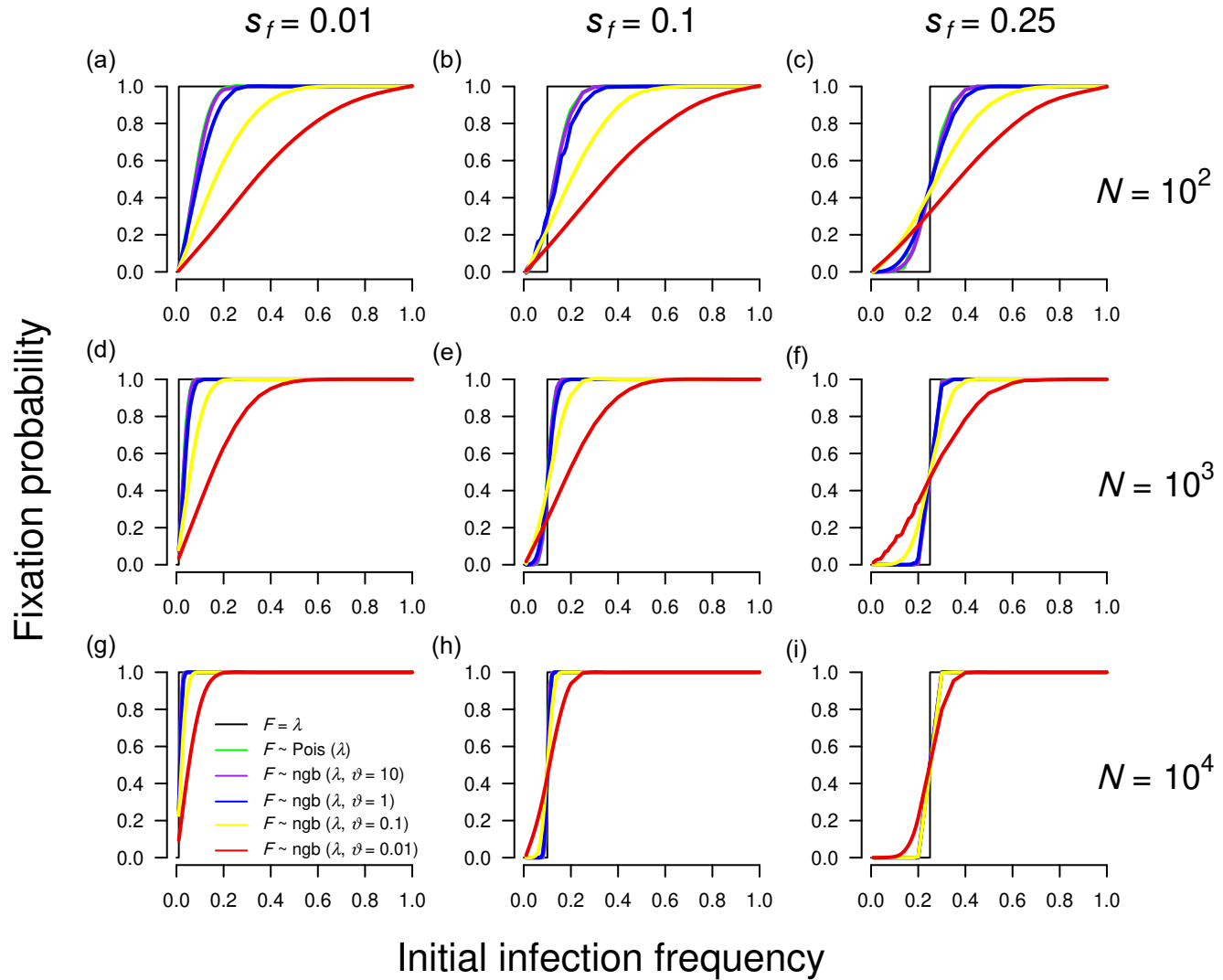
631 are also shown (dash lines). Grey area denotes the estimation for *Aedes aegypti*.

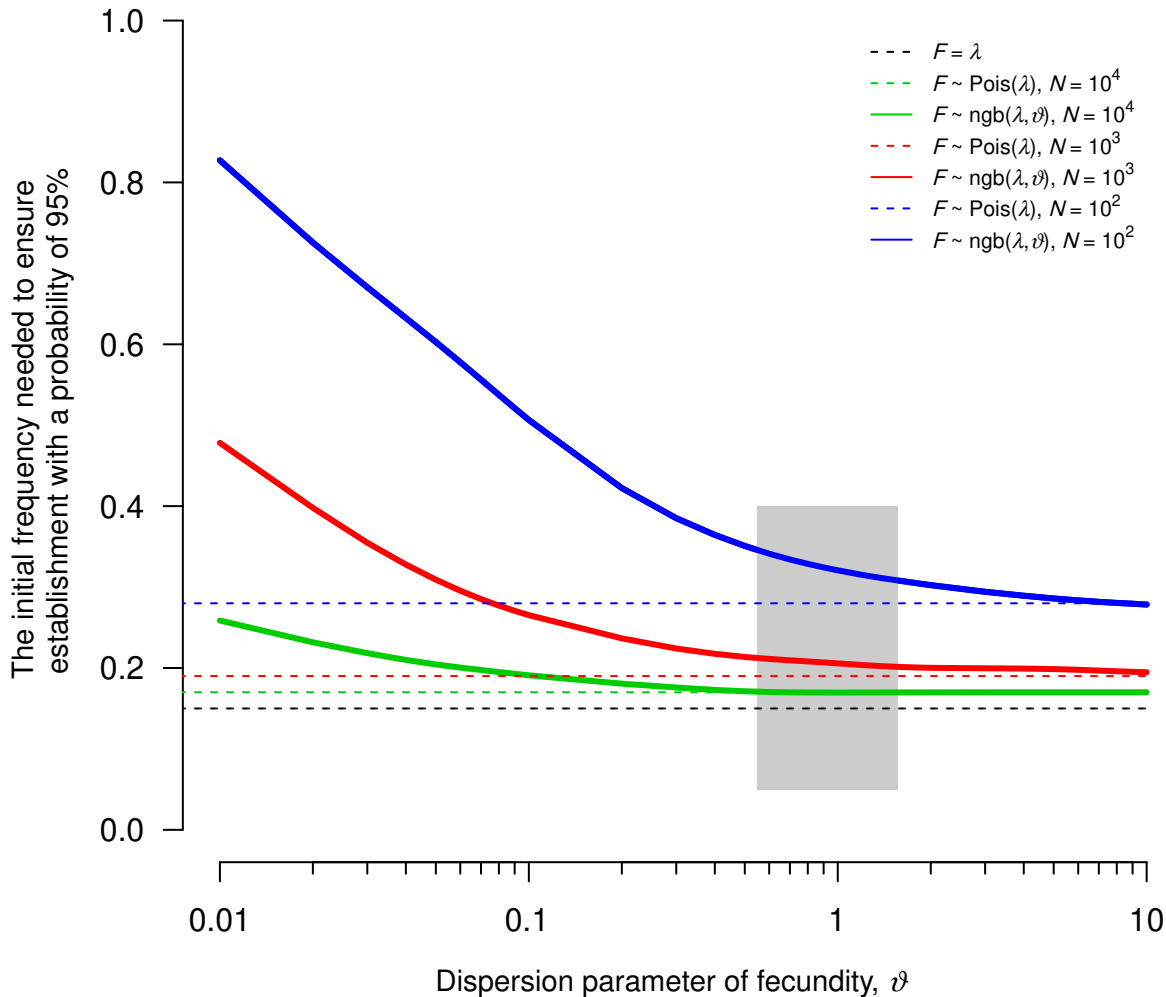
632 **Fig. 4** The fixation probability of *Wolbachia* following the introduction of a single infected
633 female into a host population of size N with different distributions of fecundity. A
634 range of parasitism costs (s) is plotted.

Aedes aegypti

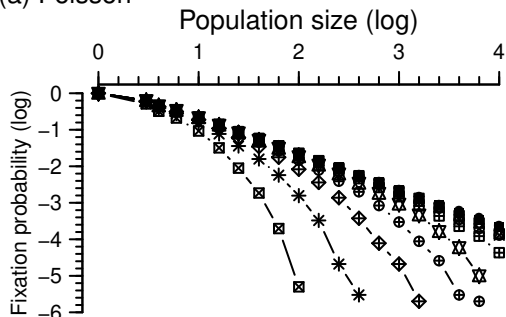
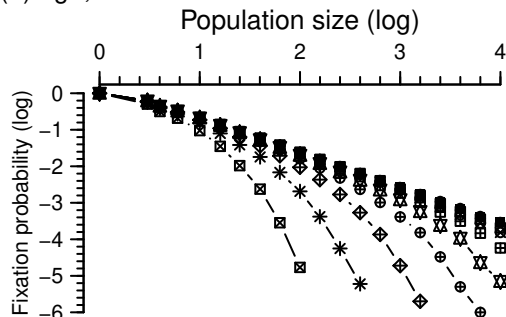
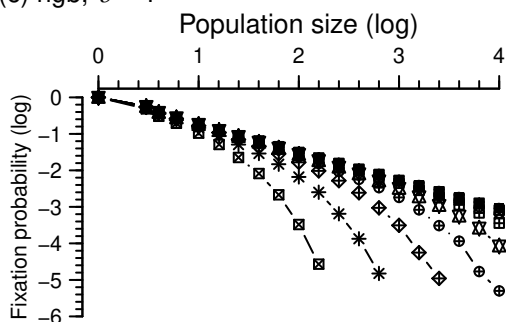
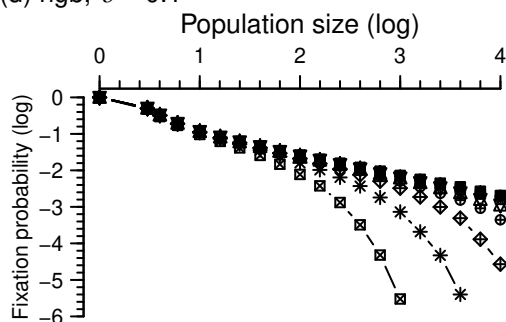
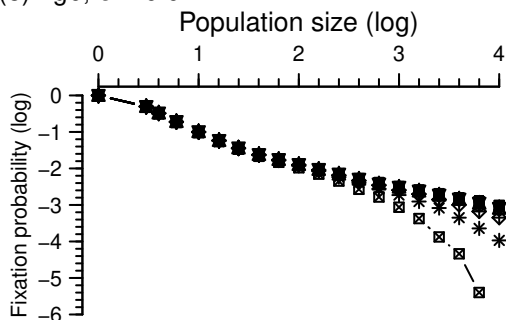


Overdispersion parameter, ϑ





(a) Poisson

(b) ngb, $\vartheta = 10$ (c) ngb, $\vartheta = 1$ (d) ngb, $\vartheta = 0.1$ (e) ngb, $\vartheta = 0.01$ 

Legends

