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1 **Predicting *Wolbachia* potential to knock down dengue virus transmission**

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11 **Abstract:**

12 Releasing mosquitoes infected with the intracellular bacteria *Wolbachia* is a
13 candidate strategy for dengue control that has recently advanced to field-testing. A
14 critical next step is to evaluate the impact of this strategy on dengue epidemiology. A
15 recent study by Ferguson and colleagues presents a mathematical framework to
16 predict the likely effect of mosquitoes carrying *Wolbachia* on dengue virus
17 transmission. Fitting the mathematical model to empirical data obtained with
18 *Wolbachia*-infected mosquitoes experimentally challenged with viremic blood from
19 dengue patients indicates that dengue virus transmission could be reduced by a
20 degree that would have a significant impact on public health.

21

22

23 **Keywords:** *Aedes aegypti*; dengue; vector competence; *Wolbachia*.

24

25 **Running title:** *Wolbachia* on the test bed

26 The failure of traditional disease prevention methods to halt the current
27 progression of dengue has promoted the development of novel entomological
28 strategies. One of the most promising approaches relies on the intracellular
29 bacterium *Wolbachia*, a bacterial symbiont commonly found in arthropods (1). The
30 main mosquito vector of dengue viruses, *Aedes aegypti*, does not naturally carry
31 *Wolbachia*, but can be experimentally transfected by embryonic microinjection (2).
32 Transinfection of *Ae. aegypti* with certain strains of *Wolbachia* results in protection
33 against dengue virus infection (3, 4). Thus, successful establishment of *Wolbachia* in
34 natural mosquito populations (5) supports a practical approach for dengue
35 suppression. The next critical step is to assess the epidemiological efficacy of
36 *Wolbachia* in reducing dengue virus transmission in the field (6).

37 A recent study by Ferguson and colleagues (7) lays the ground for future
38 efficacy trials by quantitatively predicting the likely impact of *Wolbachia* on dengue
39 virus transmission. Their study makes two significant advances. First, it provides
40 empirical data on the vector competence of *Wolbachia*-infected *Ae. aegypti* using
41 viremic blood from dengue patients and therefore more closely mimics field
42 conditions than earlier studies based on laboratory challenge with cultured virus.
43 Vector competence was evaluated by testing the presence of viral infection in the
44 mosquito abdomen and salivary glands or saliva at different time-points after the
45 infectious blood meal. Second, it develops a mathematical framework to describe the
46 dynamics of dengue virus transmission between humans and mosquitoes. The model
47 is then fitted to the empirical vector competence data to predict the effect of
48 *Wolbachia* on the basic reproduction number (R_0) of dengue virus transmission. R_0 is
49 the average number of subsequent infections resulting from an infected human
50 introduced in a naïve population. Estimates of R_0 for dengue typically range from 2 to

51 5 (8). A pathogen will go to extinction if R_0 is less than 1 because it means that each
52 infected individual will generate less than one new infection on average.

53 The study assessed the vector competence of *Ae. aegypti* mosquitoes
54 carrying one of two *Wolbachia* strains. The first strain called wMelPop is
55 characterized by high bacterial densities in mosquito tissues and results in almost
56 complete refractoriness to dengue virus infection in laboratory challenge (4).
57 However it also induces deleterious effects on mosquito fitness such as reduced
58 lifespan and blood feeding success (3, 9). Experiments using viremic blood from
59 dengue patients confirmed the strong protective effect of wMelPop against dengue
60 virus, although systemic infection was not completely blocked. Only 2.6% of
61 *Wolbachia*-infected mosquitoes had virus-positive salivary glands, compared to 90%
62 in *Wolbachia*-free controls. The authors concluded that wMelPop would result in at
63 least 90% blocking of transmission. The second *Wolbachia* strain called wMel infects
64 mosquito tissues at lower densities, and induces resistance to dengue virus infection
65 in laboratory challenge, although to a lesser extent than wMelPop, and in the
66 absence of major fitness costs (10). Consistently, there was significant but imperfect
67 virus blocking in mosquitoes infected by wMel challenged with viremic blood from
68 dengue patients. Although viral load measured in the abdomen was at least 10-fold
69 lower in *Wolbachia*-infected mosquitoes, most of the blocking effect was observed
70 during viral dissemination from the abdomen to the saliva. The effect comprised a net
71 reduction of the probability of saliva infection, and a slight lengthening of the time
72 required for the virus to reach saliva.

73 Ferguson *et al.* (7) then used the empirical data generated in their vector
74 competence assays as well as clinical records of viremia levels in patients to inform a
75 newly developed mathematical model of dengue virus transmission (Fig. 1). The

76 model was designed to evaluate the effect of *Wolbachia* on dengue virus
77 transmission based on the comparison of R_0 in a mosquito population with or without
78 *Wolbachia*. The modeling approach only considered wMel because wMelPop did not
79 require mathematical modeling to predict quasi-complete blocking of transmission.
80 The mosquito infection model consisted of a relatively simple dose-response model
81 of abdomen infection probability as a function of viremia coupled to a model of saliva
82 infection probability as a function of viremia as well as time elapsed since the blood
83 meal (Fig. 1). Model fitting to the empirical data was performed separately for each of
84 the four dengue virus serotypes. The baseline scenario predicted 66 to 75% of
85 reduction in R_0 depending on the dengue serotype. Other scenarios were considered
86 to account for the uncertainty in model parameters that were not directly informed by
87 empirical data such as the minimum infectious dose for successful mosquito-to-
88 human transmission. The percentage in R_0 reduction varied from 40 to 80% among
89 serotypes under the alternative scenarios. Therefore, under the baseline model, a
90 *Wolbachia* intervention using the wMel strain is expected to result in two thirds to
91 three quarters less secondary infections from an initial case. This means that the
92 intervention would achieve elimination of dengue for initial R_0 values of 3 or 4,
93 respectively. Thus, *Ae. aegypti* mosquitoes carrying wMel could reduce dengue virus
94 transmission by a degree that would have considerable public health impact, possibly
95 leading to dengue elimination where transmission is low to moderate (8).

96 A major strength of the Ferguson *et al.* study (7) is the use of state-of-the-art
97 methods to evaluate vector competence. Historically, methods of determining vector
98 competence have been largely restricted to artificial infectious blood meals
99 composed of animal blood spiked with virus grown in cell culture. These artificial
100 methods have limited our ability to extrapolate to natural transmission and to

101 understand the significance of data from epidemiological studies with humans (11).
102 Recent studies from the same group overcame this obstacle by developing vector
103 competence assays that expose mosquitoes to the blood of naturally infected,
104 viremic humans (12). Although in the present study viremic blood was presented to
105 mosquitoes in an artificial feeder through a skin-simulating membrane, it is
106 reasonable to consider this indirect mosquito feeding method as a good proxy of
107 direct feeding through the skin of a person. Nevertheless, vector competence is only
108 one of several parameters that influence dengue virus transmission by mosquitoes
109 (11). It will be necessary in future studies to evaluate the effect of wMel on several
110 important entomological parameters that Ferguson *et al.* did not examine in their
111 study such as blood feeding behavior and longevity. For instance, a shorter lifespan
112 could act to further reduce dengue virus transmission. Conversely, increased blood
113 feeding frequency would enhance transmission. The wMelPop strain confers very
114 strong protection against dengue virus infection and further limits transmission by
115 shortening the mosquito lifespan (3, 4, 13). But the life-shortening effect would
116 represent a significant hurdle to establishing wMelPop infection in a natural *Ae.*
117 *aegypti* population by reducing competitiveness against wild mosquitoes. Overall, the
118 costs and benefits of each *Wolbachia* strain will have to be carefully balanced prior to
119 field releases.

120 One limitation of the Ferguson *et al.* study (7) is that the transmission model
121 relies on a distribution of viral titers in plasma that may not accurately reflect reality,
122 for at least two reasons. First, the empirical distribution of plasma viremia levels that
123 were used to develop the transmission model only included hospitalized and
124 ambulatory patients. This distribution, therefore, did not consider inapparent
125 (subclinical) infections that are believed to represent the majority of dengue infections

126 (14). People with inapparent infections are usually assumed to inefficiently infect
127 mosquitoes because they do not reach sufficiently high viremia levels, but this
128 assumption has not been verified (15). Second, the transmission model did not
129 account for the epidemiological feedback. Put simply, introduction of *Wolbachia*-
130 infected mosquitoes could affect the distribution of viremia levels in humans, and
131 consequently modify the baseline parameters underlying the model that estimates
132 transmission. The authors considered that modeling three distributions recapitulates
133 the complete transmission cycle (Fig. 1): human viremia level, human-to-mosquito
134 transmission probability (abdomen infection), and mosquito-to-human transmission
135 probability (saliva infection). In fact, a parameter characterizing the relationship
136 between mosquito-to-human transmission and the resulting viremia profile is missing
137 from the cycle. One could imagine, for instance, that *Wolbachia*-infected mosquitoes
138 inoculate smaller infectious doses that result in shorter, shallower viremia profiles. In
139 both cases, fortunately, these shortcomings likely contributed to underestimate the
140 impact of *Wolbachia* on dengue virus transmission. Indeed, the transmission blocking
141 effect of *Wolbachia* would be stronger if viremia levels were reduced compared to
142 those seen in dengue-infected people with clinical symptoms.

143 Taken together, this work and previous studies support the idea that
144 *Wolbachia* has a realistic potential to knock down dengue virus transmission in the
145 field. It is also clear, however, that *Wolbachia* alone will not be sufficient to effectively
146 control dengue, especially in settings where transmission is high. In addition to novel
147 vector population suppression strategies (16) and vaccines (17), *Wolbachia* may
148 soon enrich the arsenal to effectively fight against dengue.

149

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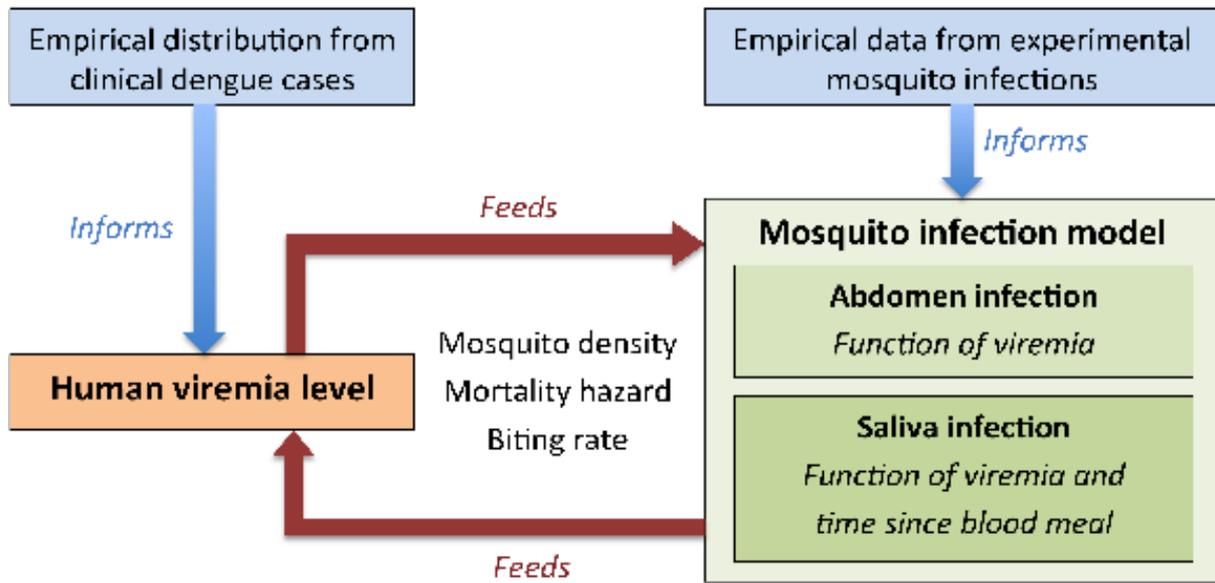
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202 **Figure 1. Diagram of the transmission model.**



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