Modeling the transmission of *Wolbachia* in mosquitoes for controlling mosquito-borne diseases

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Outlines

"Mosquitoes cause more human suffering than any other organism."

– American Mosquito Control Association

- dengue fever: flu-like illness: high fever, muscle and joint pains; severe cases: serious bleeding and shock, may be life-threatening
- chikungunya: similar clinical signs, debilitating joint pain, may persist for several months, or even years; can be misdiagnosed
- Zika: no or only mild symptoms; infection during pregnancy can cause microcephaly in the baby (birth defect in brain)

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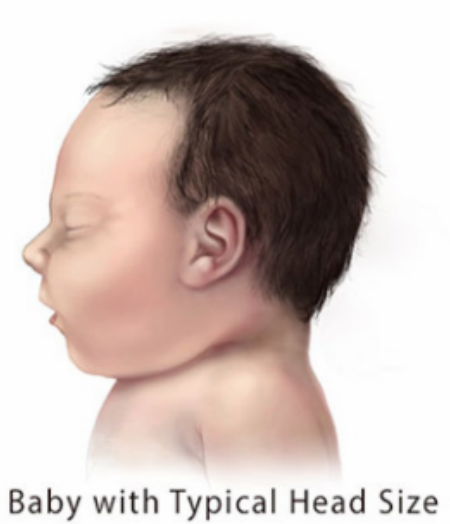
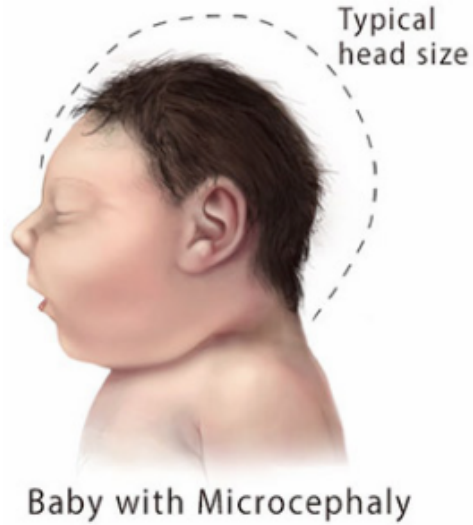


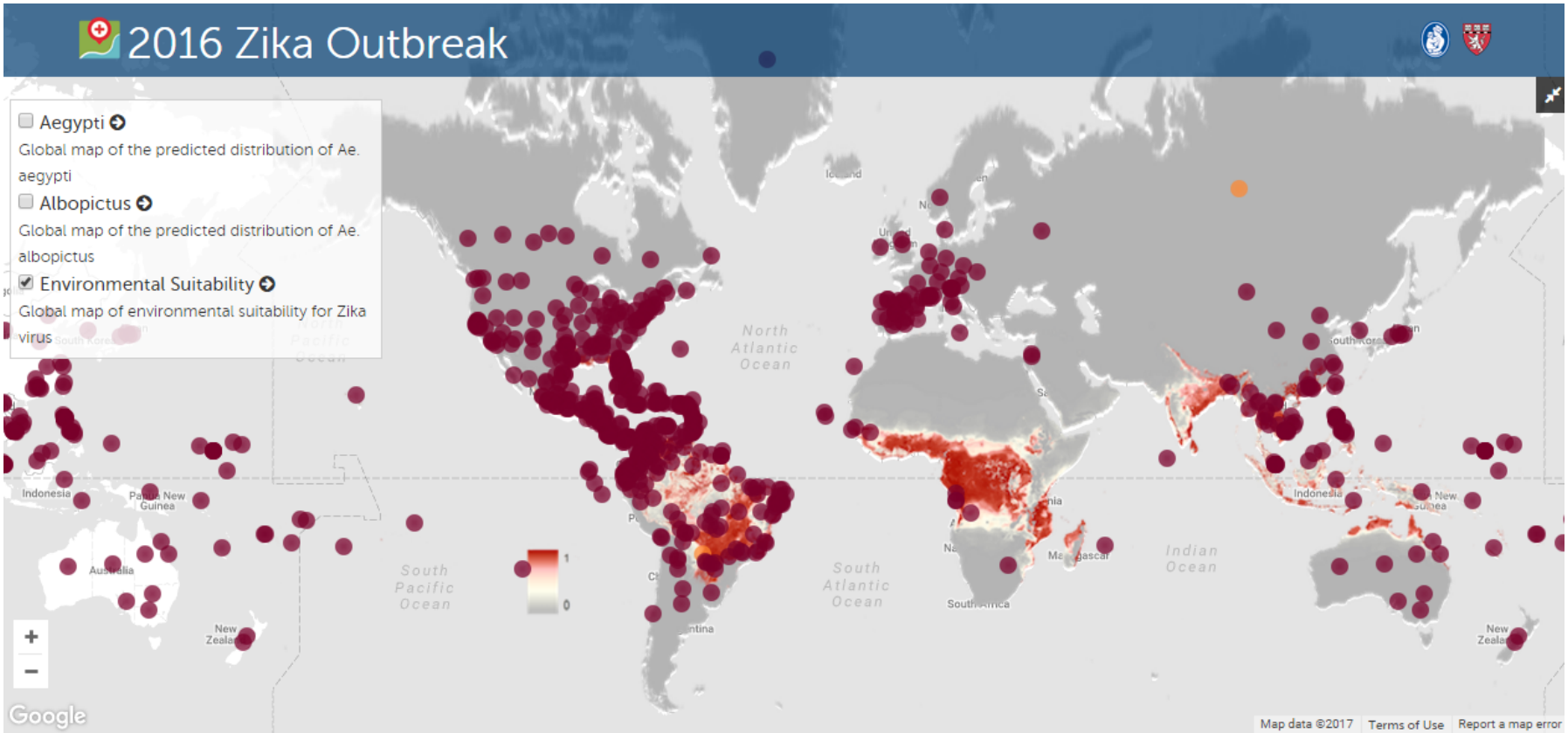
Baby with Typical Head Size



Baby with Microcephaly

Source: https://www.cdc.gov/ncbddd/birthdefects/microcephaly.html

Areas with Risk of Zika



Source: `http://www.healthmap.org/zika/#timeline`

- Central and South America, sub-Saharan Africa, Southeast Asia, etc...

Aedes aegypti – primary vector for the transmission

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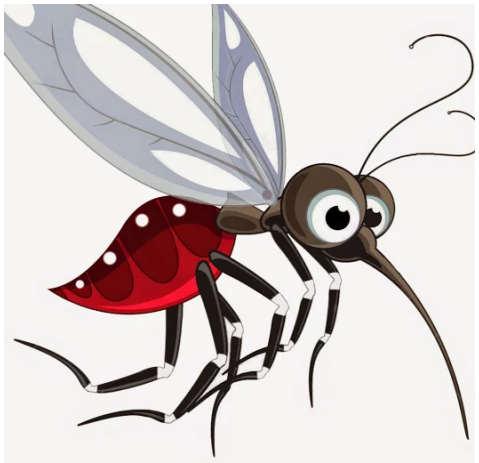

Aedes aegypti

mitigation approaches:

- spraying of insecticide (mostly used)
  - financial cost can be prohibitively high
  - logistically difficult in urban/remote areas
  - evolution of resistance
- remove breeding habitats
  - water tank/scrap tires
- introduce natural predators
  - fish to control larvae
- sterile insect technique (SIT)
  - release sterilized male mosquitoes
  - not self-replicating, reduced competitiveness

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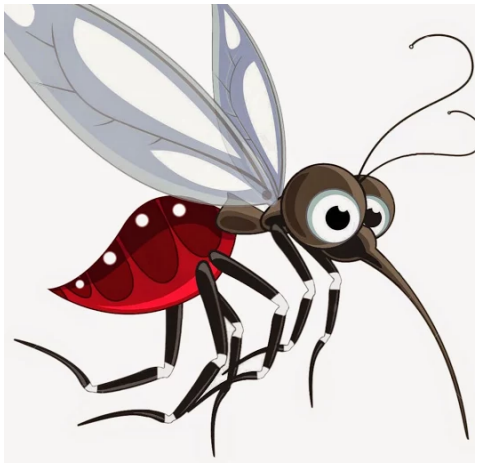

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$\Rightarrow$ reduce the mosquito population size

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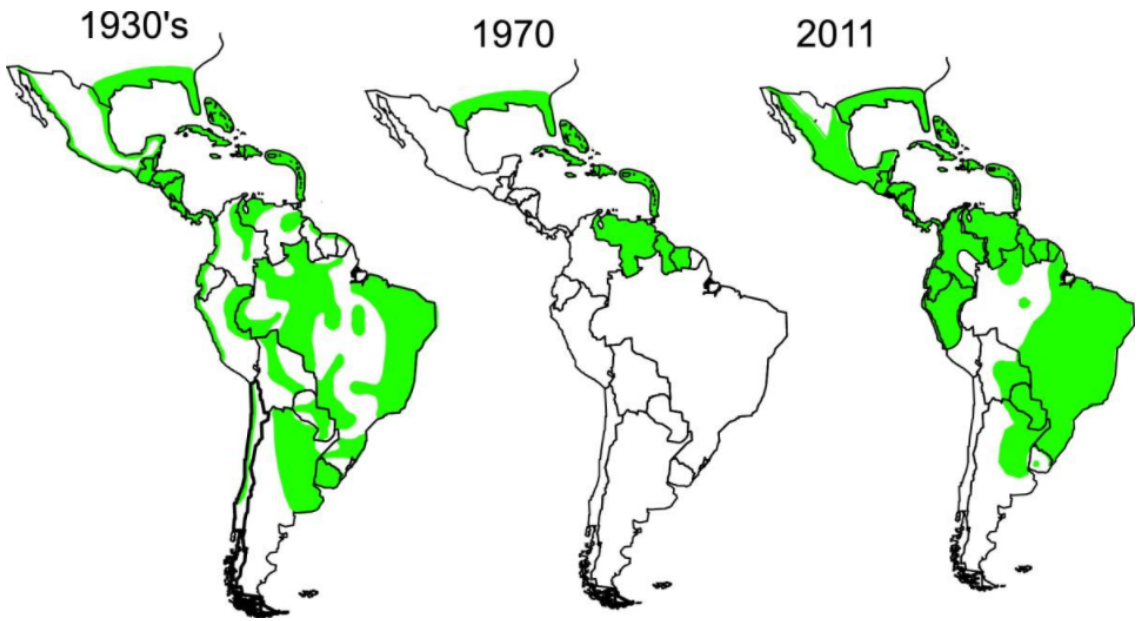

Reinfestation of tropical America by Aedes aegypti, 1930 - 2011

Source: Gubler DJ. Dengue, Urbanization and Globalization: The Unholy Trinity of the 21st Century. *Tropical Medicine and Health*. 2011; 39(4 Suppl):3-11.

Wolbachia – fight an epidemic with an epidemic

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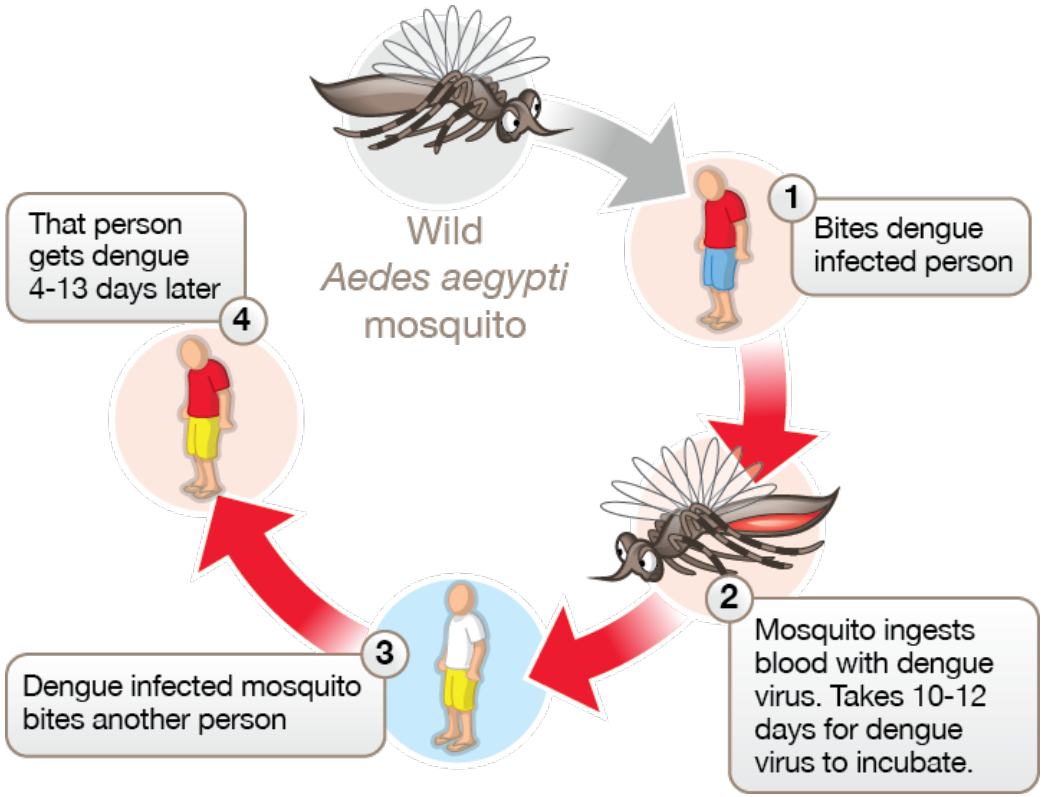

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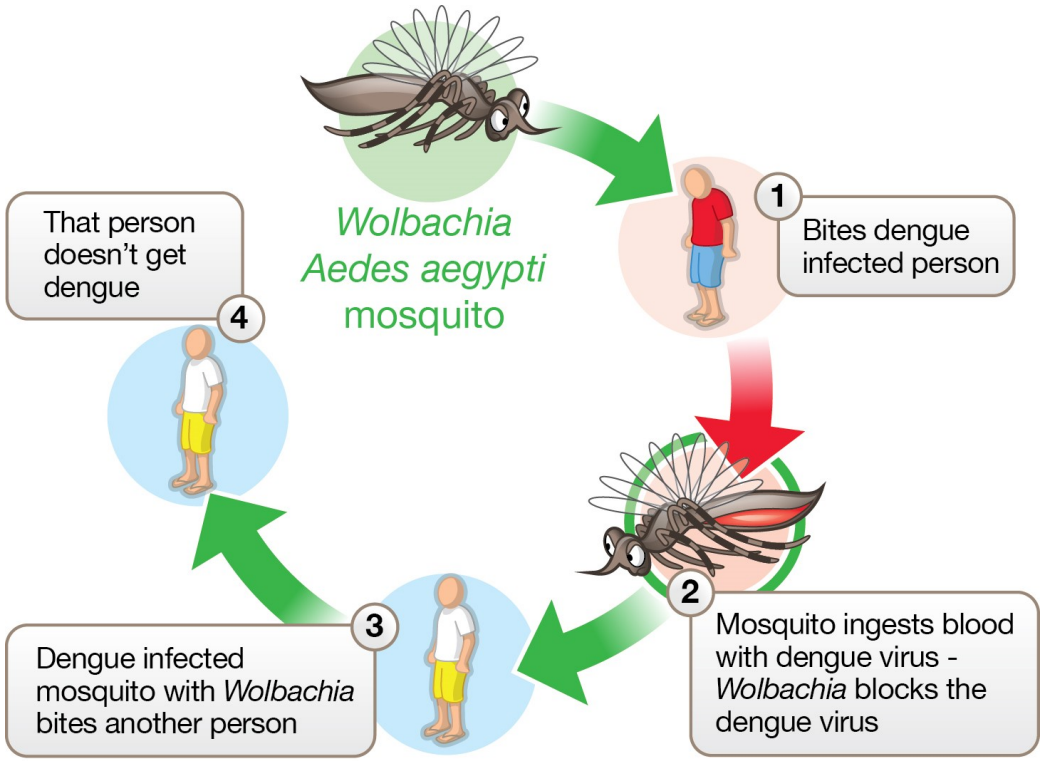

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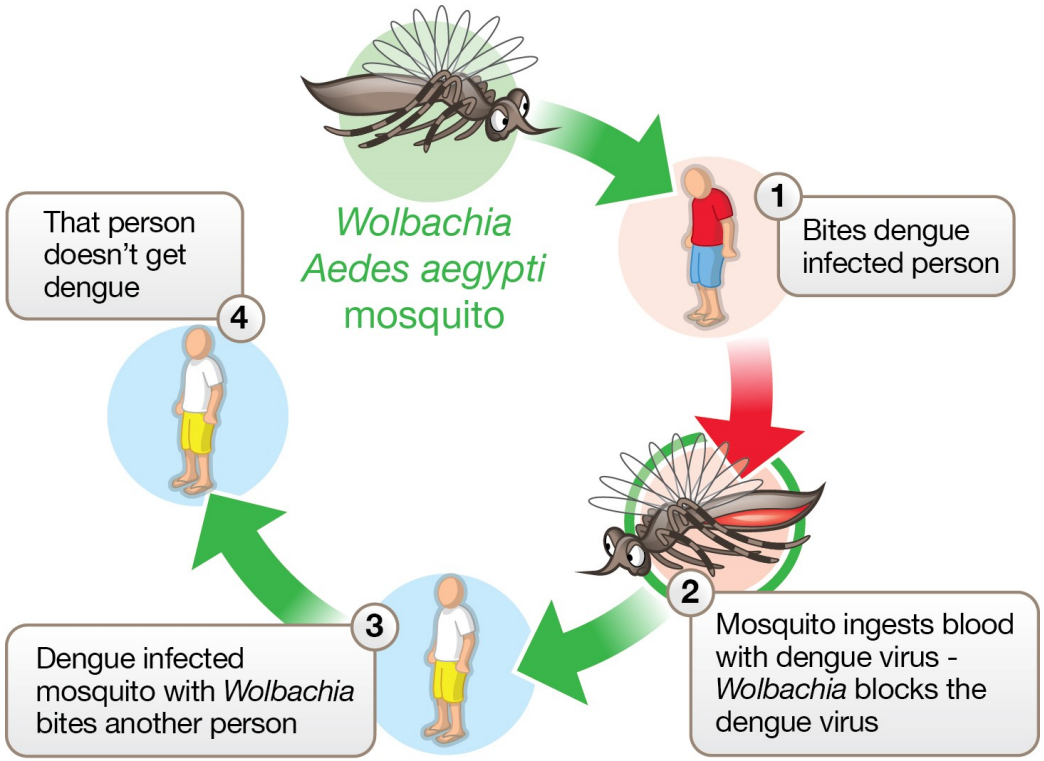

- *Wolbachia* blocks the disease transmission to human

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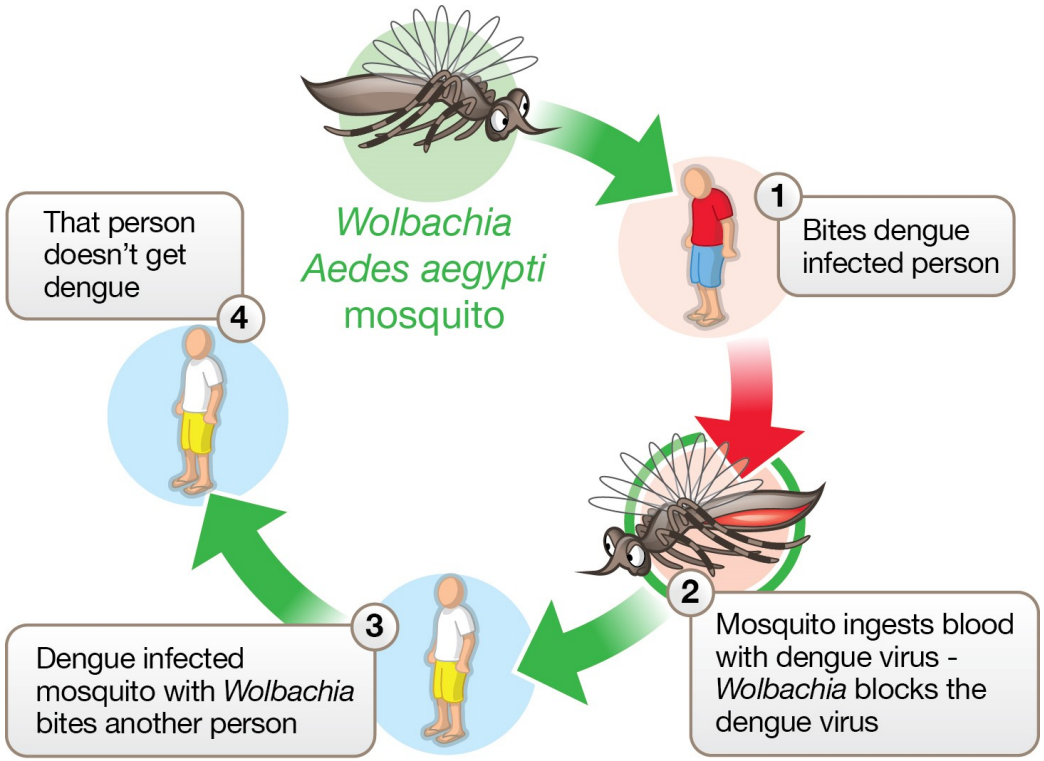

- *Wolbachia* blocks the disease transmission to human
- field trials in Australia, Brazil, Columbia, Indonesia, Vietnam to suppress dengue/Zika transmission with promising results

source: Australias Department of Foreign Affairs and Trade (DFAT) & Eliminate Dengue Program

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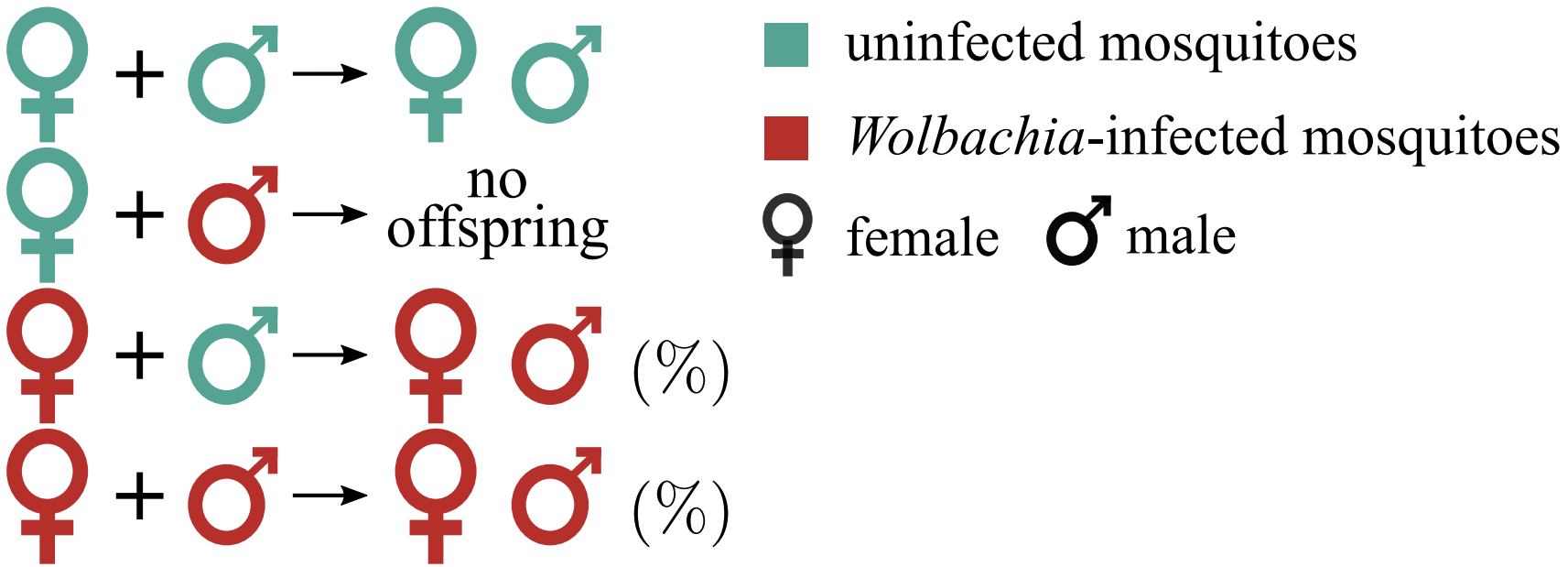
Schematic of the complex maternal transmission mating



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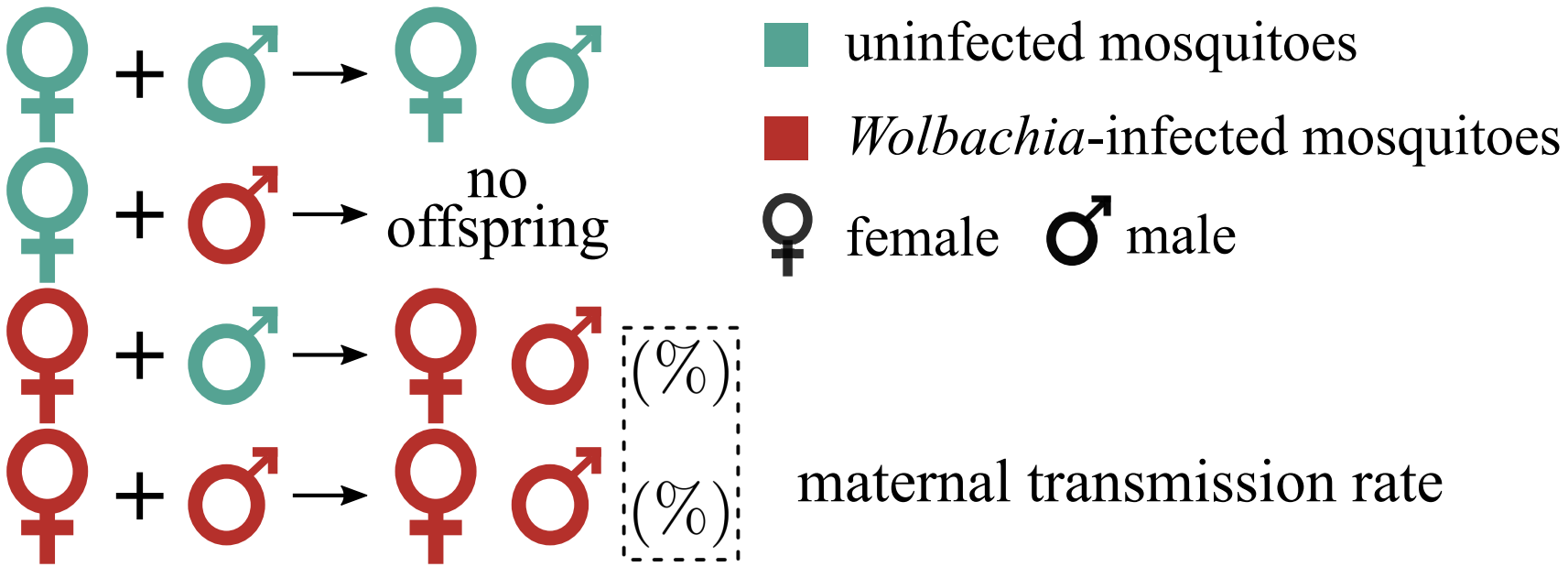

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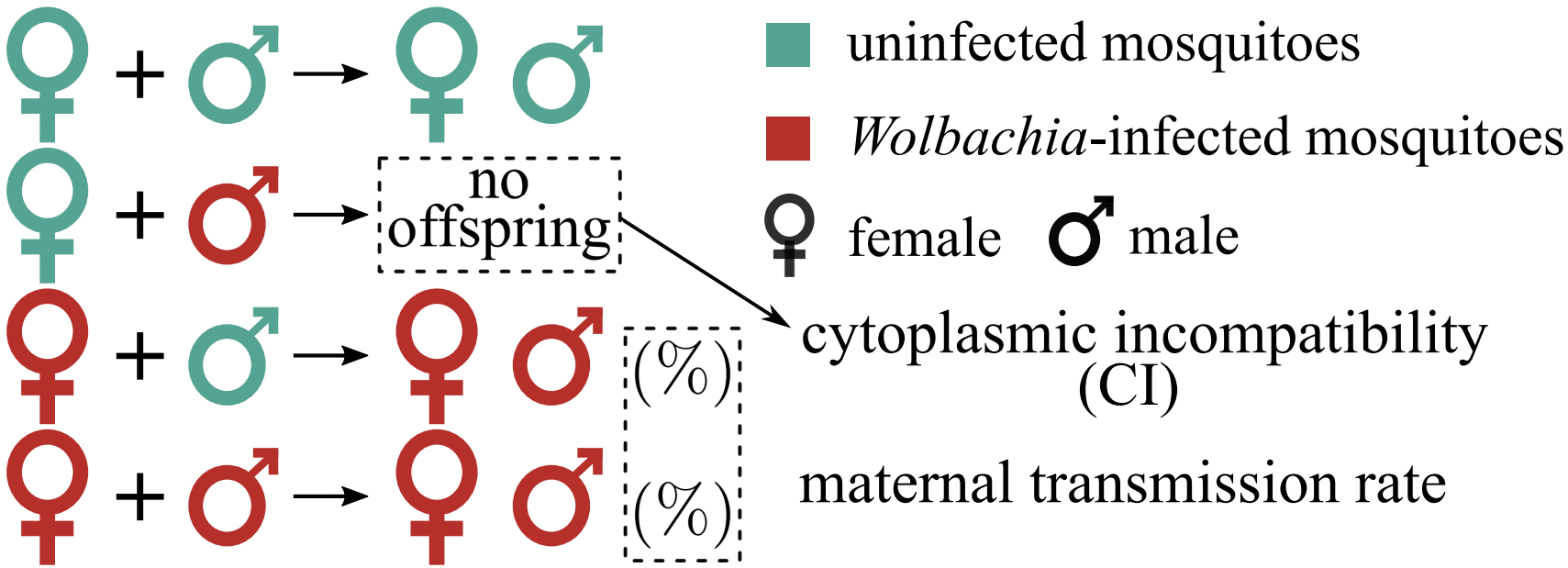

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If there is a tipping point, beyond which the infection could take off?

Critical threshold condition can be quantified with a Mathematical model

$$\frac{\textit{Wolbachia}\text{-infected mosquitoes}}{\text{uninfected mosquitoes}} \begin{cases} < \theta, & \text{infection dies out} \\ > \theta, & \text{stable infection} \end{cases}$$

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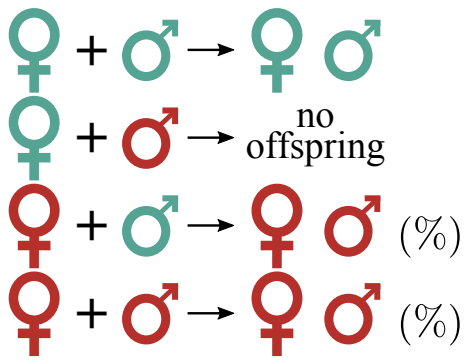
- develop an ODE model to describe the complex transmission cycle
- analyze the threshold condition for having a stable endemic *Wolbachia*

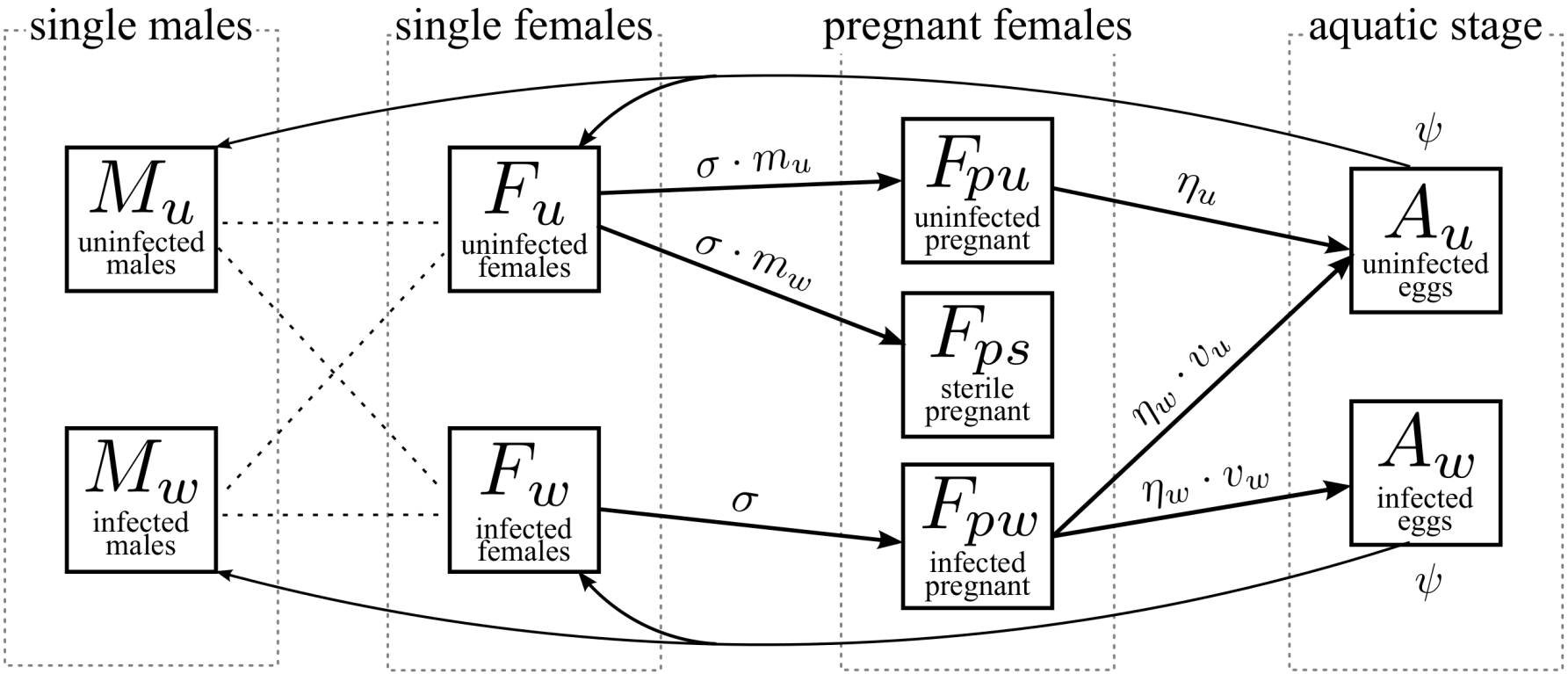
Outlines

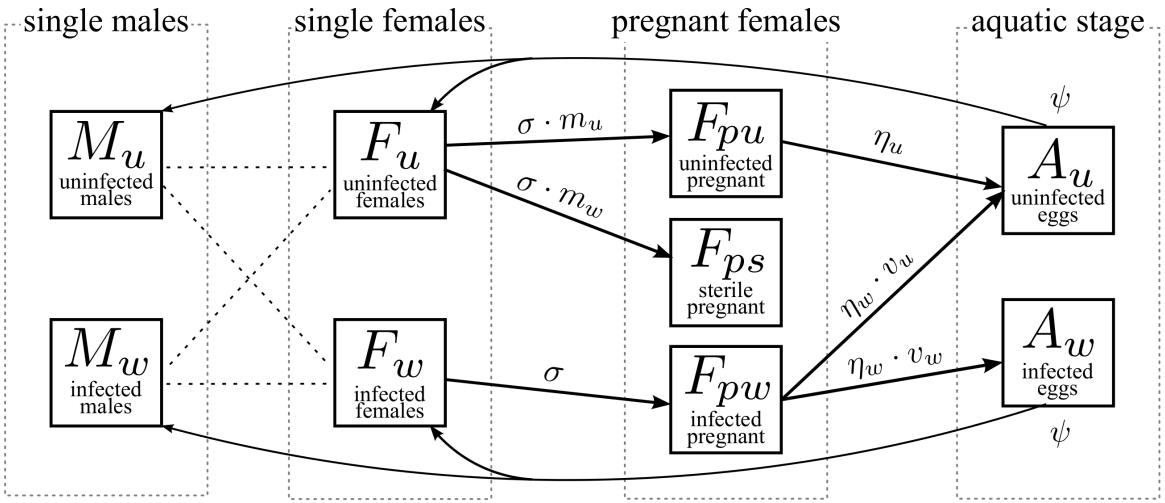
Our new model captures the complex transmission cycle

by accounting for ...

- two-sex transmission
- multi-stage female life cycle
- carrying capacity for aquatic stage







σ: mating rate

m_w: prop. infected males

η_w/η_u: procreation rates

v_w: maternal transmission

ψ: egg developing rate

single males
$$\begin{cases} \dot{M}_u = b_m \psi A_u - \mu_{mu} M_u \\ \dot{M}_w = b_m \psi A_w - \mu_{mw} M_w \end{cases}$$

single females
$$\begin{cases} \dot{F}_u = b_f \psi A_u - (\sigma + \mu_{fu}) F_u \\ \dot{F}_w = b_f \psi A_w - (\sigma + \mu_{fw}) F_w \end{cases}$$

pregnant females
$$\begin{cases} \dot{F}_{pu} = \sigma \dfrac{M_u}{M_u + M_w} F_u - \mu_{fu} F_{pu} \\ \dot{F}_{pw} = \sigma F_w - \mu_{fw} F_{pw} \end{cases}$$

aquatic stage
$$\begin{cases} \dot{A}_u = (\phi_u F_{pu} + v_u \phi_w F_{pw}) \left(1 - \dfrac{A_u + A_w}{K_a}\right) - (\mu_a + \psi) A_u \\ \dot{A}_w = v_w \phi_w \left(1 - \dfrac{A_u + A_w}{K_a}\right) F_{pw} - (\mu_a + \psi) A_w \end{cases}$$

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Three types of equilibria (steady states)

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- **Endemic Equilibrium (EE)**
  - infected and uninfected mosquitoes coexist in the population

$$EE = (A_u^*, A_w^*, F_u^*, F_w^*, F_{pu}^*, F_{pw}^*, M_u^*, M_w^*)$$

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For *Wolbachia* infection in mosquito population,

$$\mathbb{R}_0 = \ ?$$

Calculation of $\mathbb{R}_0$ for *Wolbachia*

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$$\mathbf{X}'(t) = \mathcal{F} - \mathcal{V} = \text{rate of new infection} - \text{rate of transition}$$

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$$\mathbb{R}_0 = v_w \frac{\mu_{fu}\,\phi_w\,(\sigma + \mu_{fu})}{\mu_{fw}\,\phi_u\,(\sigma + \mu_{fw})}$$

v_w	maternal transmission rate
μ_{fu}	death rates for F_u, F_{pu}
μ_{fw}	death rates for F_w, F_{pw}
ϕ_u	egg-laying rate for F_{pu}
ϕ_w	egg-laying rate for F_{pw}
σ	mating rate

Next generation numbers for infected and uninfected population

- $\mathbb{G}_{0u}$ (next generation number for the uninfected population): the number of uninfected eggs that one uninfected egg can generate

$$A_u \rightarrow F_u \rightarrow F_{pu} \rightleftarrows A_u$$

develops mates produces

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- $\mathbb{G}_{0w}$ (next generation number for the infected population): the number of infected eggs that one infected egg can generate

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$$\mathbb{G}_{0w} = v_w b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fw}} \frac{\phi_w}{\mu_{fw}}$$

Basic reproductive number as the ratio of the next generation numbers

$$\mathbb{G}_{0u} = b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fu}} \frac{\phi_u}{\mu_{fu}} \quad \text{(uninfected)}$$

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$$= \underbrace{\left(v_w b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fw}} \frac{\phi_w}{\mu_{fw}} \right)}_{\mathbb{G}_{0w}} \Big/ \underbrace{\left(b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fu}} \frac{\phi_u}{\mu_{fu}} \right)}_{\mathbb{G}_{0u}}$$

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$$\mathbb{G}_{0w} = v_w b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fw}} \frac{\phi_w}{\mu_{fw}} \quad \text{(infected)}$$

$$\mathbb{R}_0 = v_w \frac{\mu_{fu}\,\phi_w\,(\sigma + \mu_{fu})}{\mu_{fw}\,\phi_u\,(\sigma + \mu_{fw})}$$

$$= \underbrace{\left(v_w b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fw}} \frac{\phi_w}{\mu_{fw}} \right)}_{\mathbb{G}_{0w}} \Bigg/ \underbrace{\left(b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fu}} \frac{\phi_u}{\mu_{fu}} \right)}_{\mathbb{G}_{0u}}$$

$$= \frac{\#\text{ of new infected eggs}}{\#\text{ of new uninfected eggs}} \quad \text{(per egg within one life cycle)}$$

$\mathbb{R}_0$ v.s. Stability analysis

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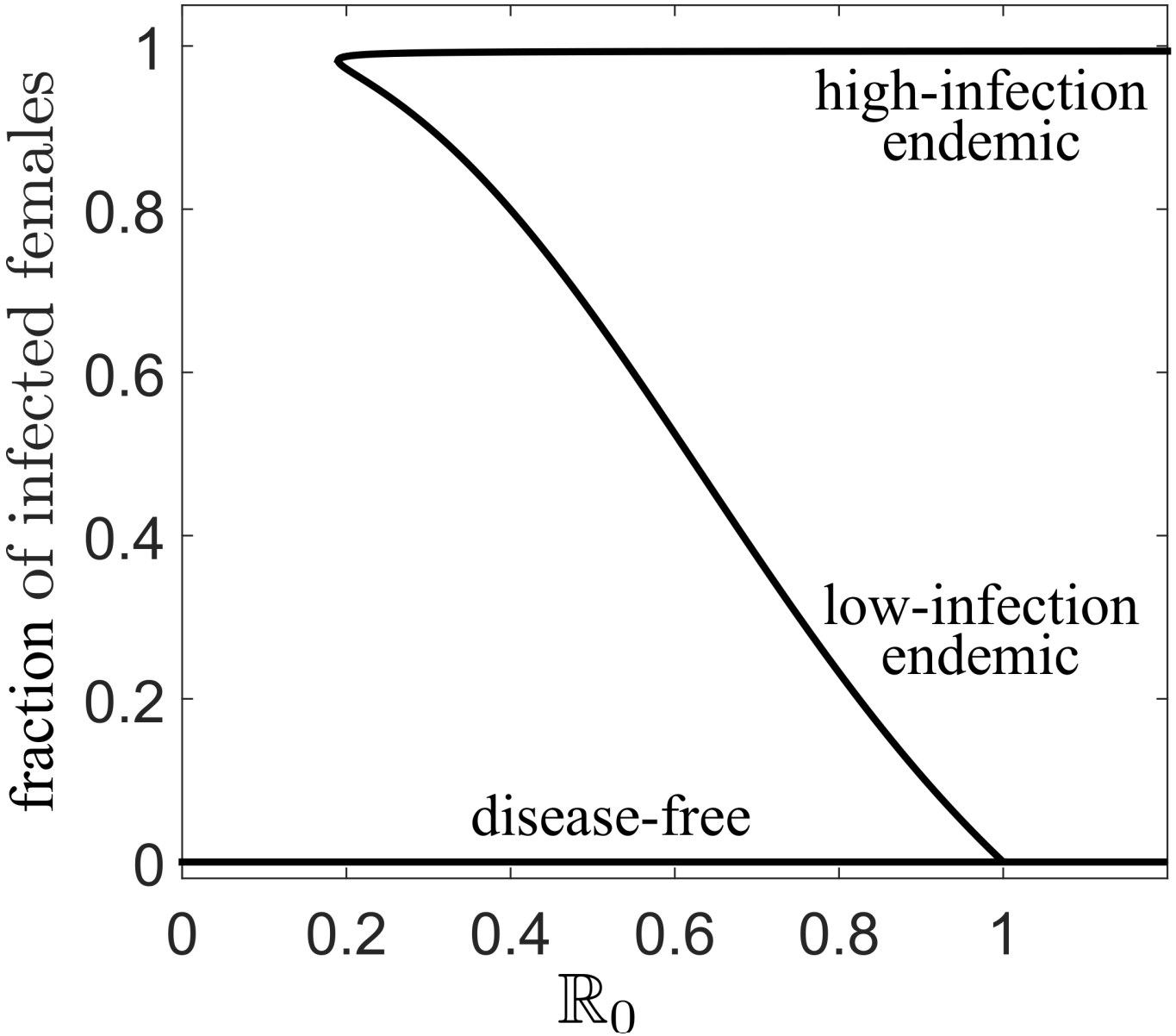
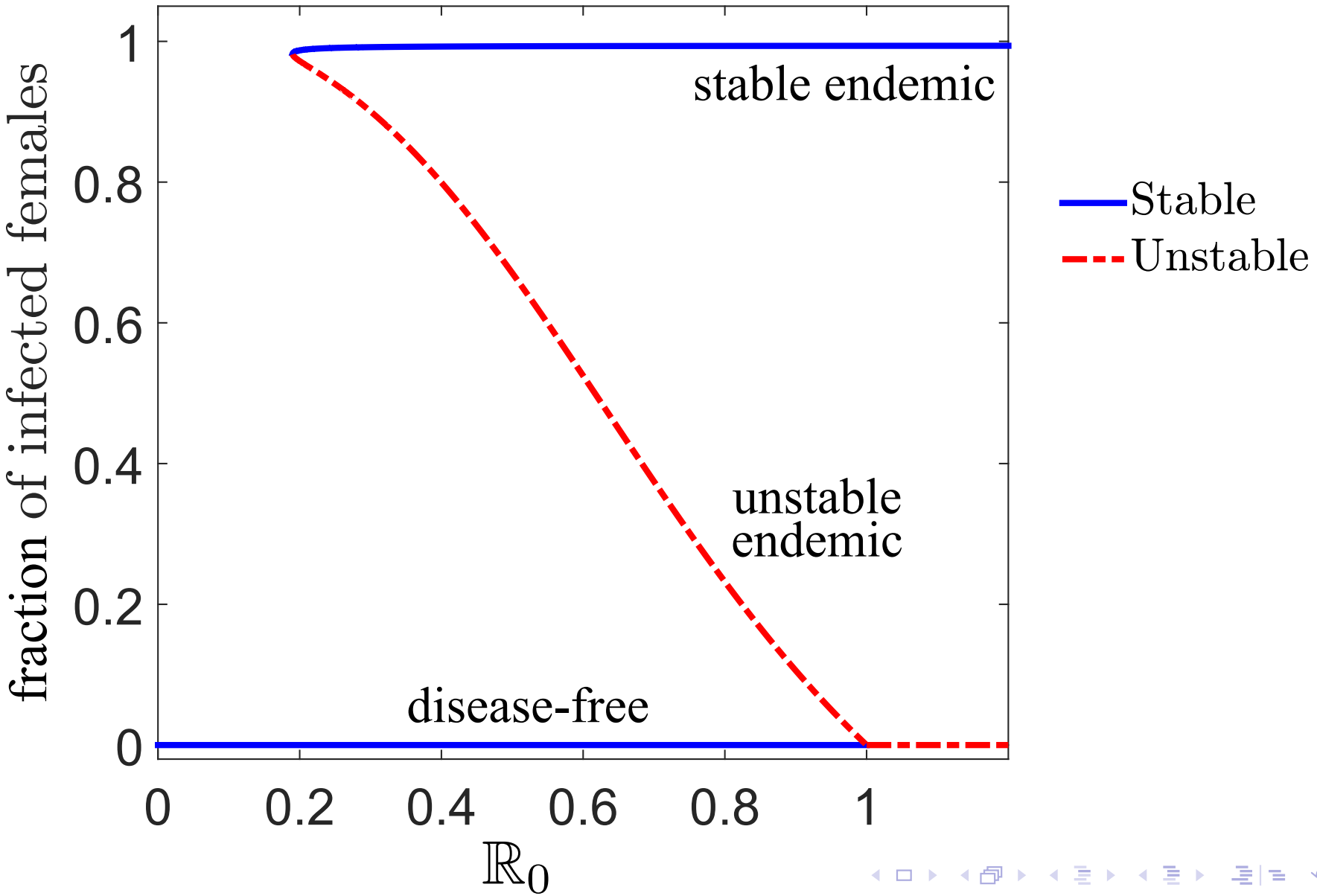
  - There is a critical threshold for *Wolbachia* endemic to be possible.

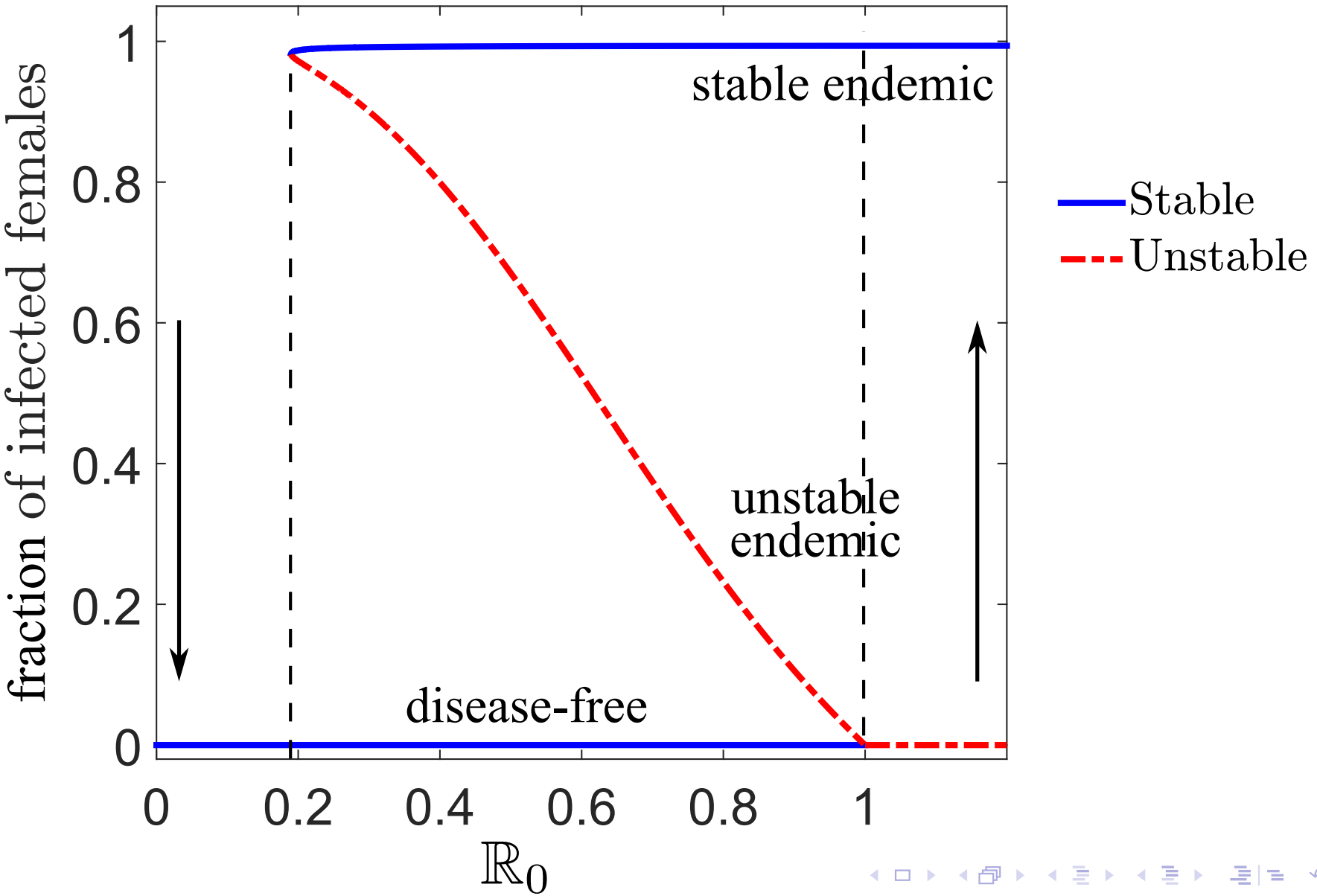
Three steady states for imperfect maternal transmission



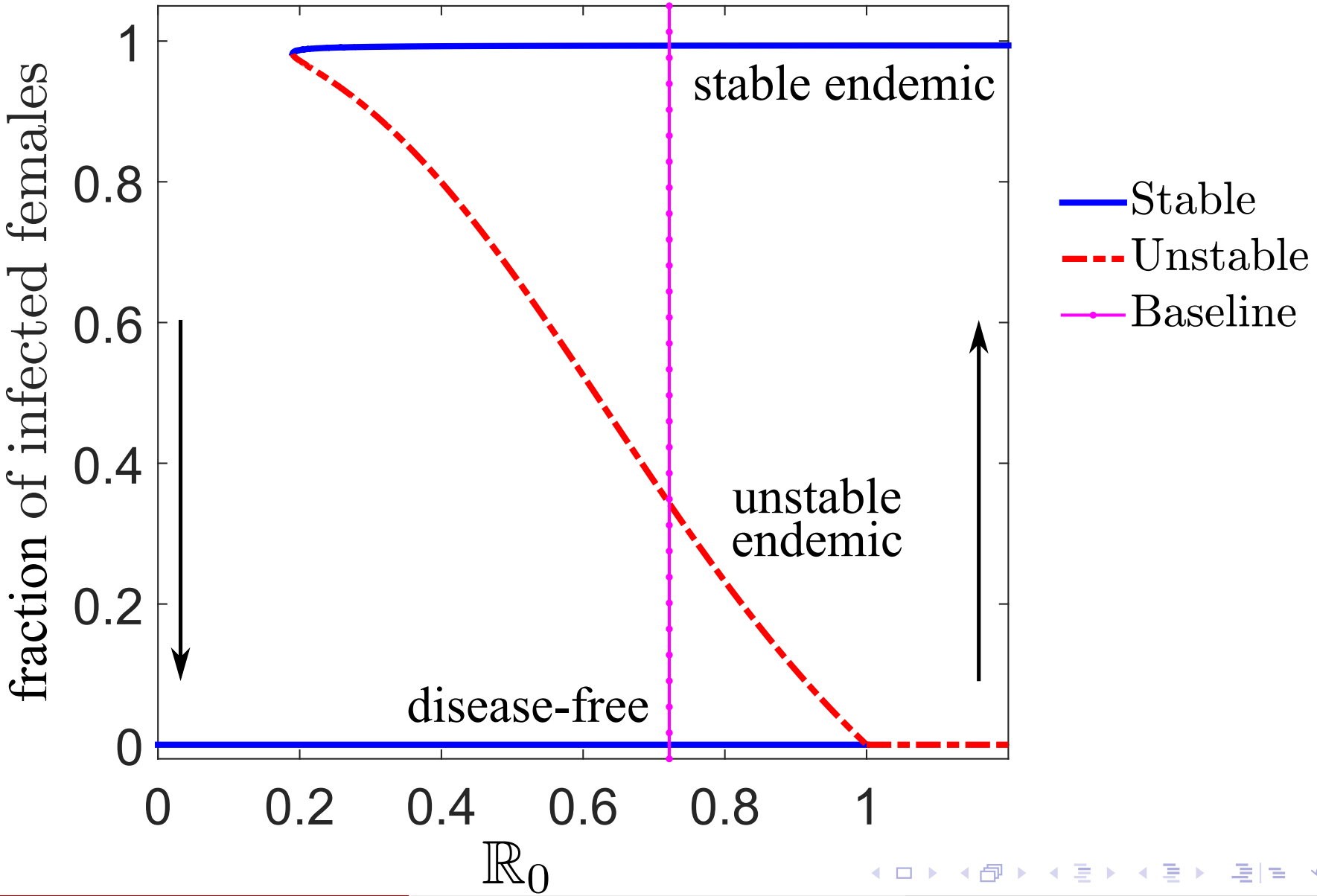
Stability analysis on the system gives ...



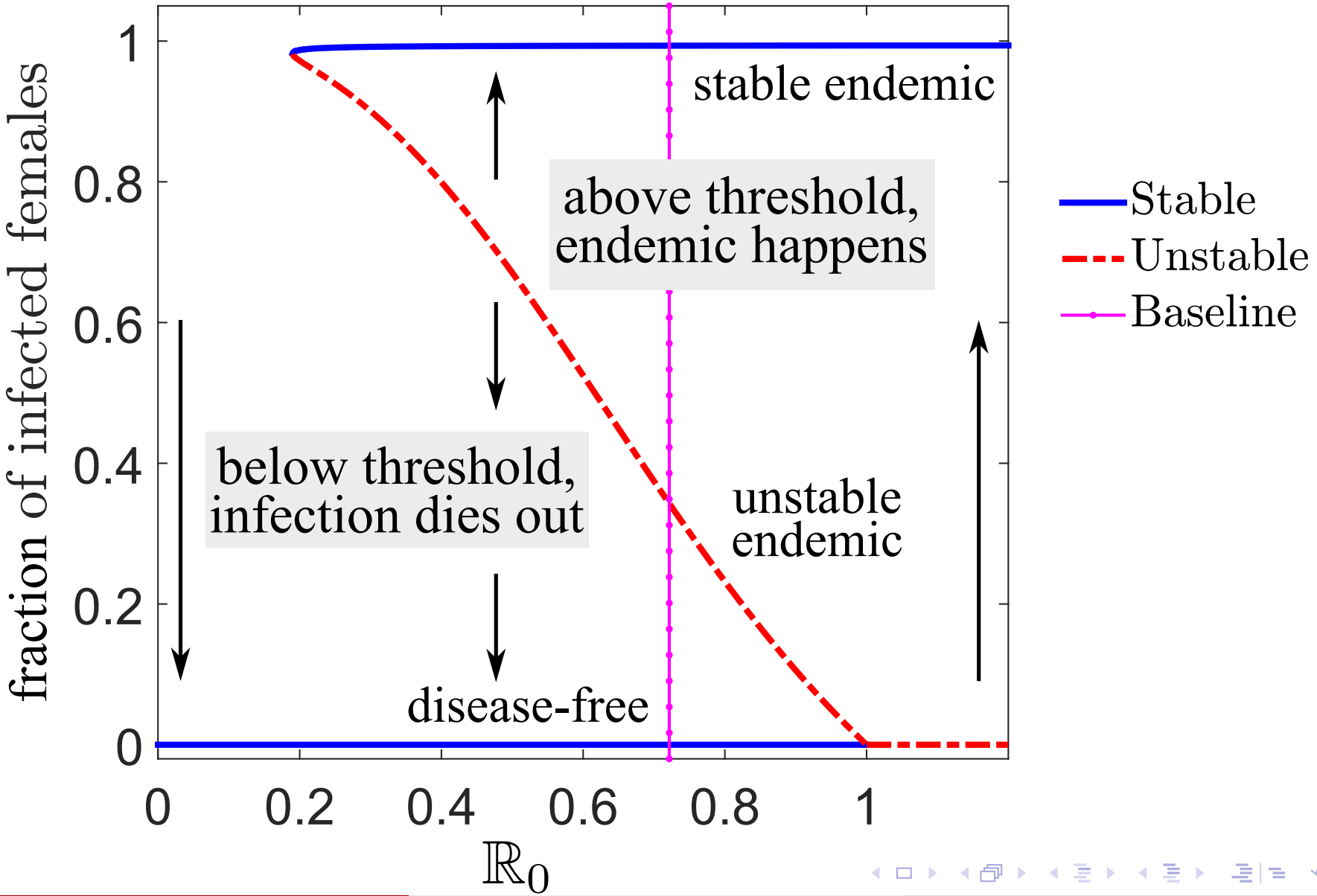
When $\mathbb{R}_0$ is very small OR $\mathbb{R}_0 > 1$ ...



However, $\mathbb{R}_0$ for real world...

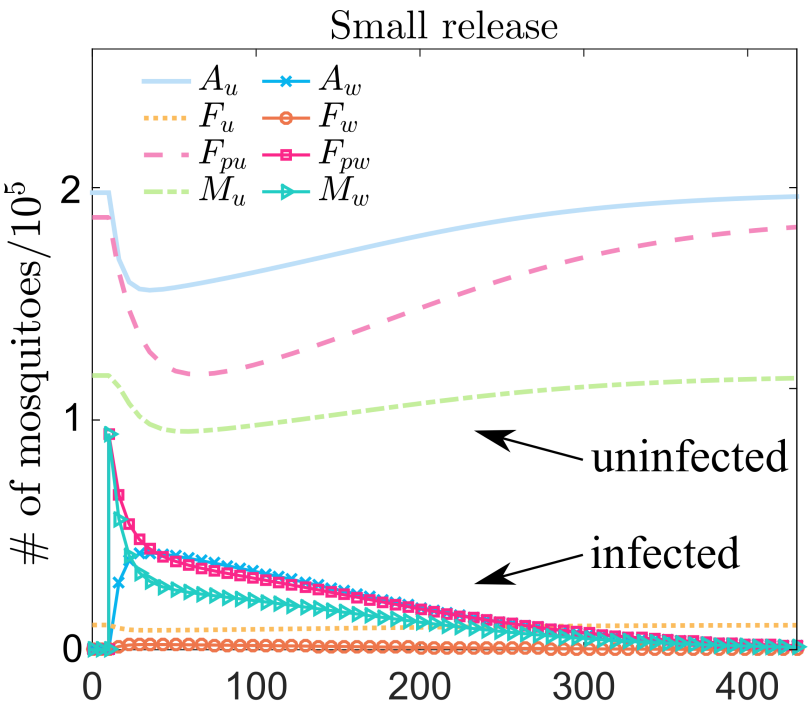


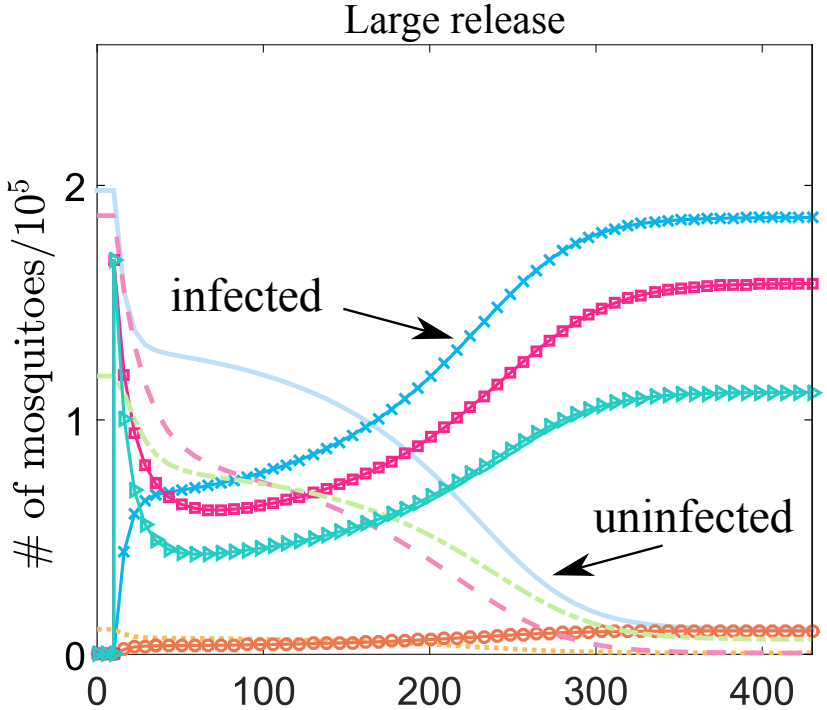
Critical threshold for having *Wolbachia* endemic



Outlines

Numerical verification of the threshold condition





Small release $\Rightarrow$ infection dies out

Large release $\Rightarrow$ infection persists

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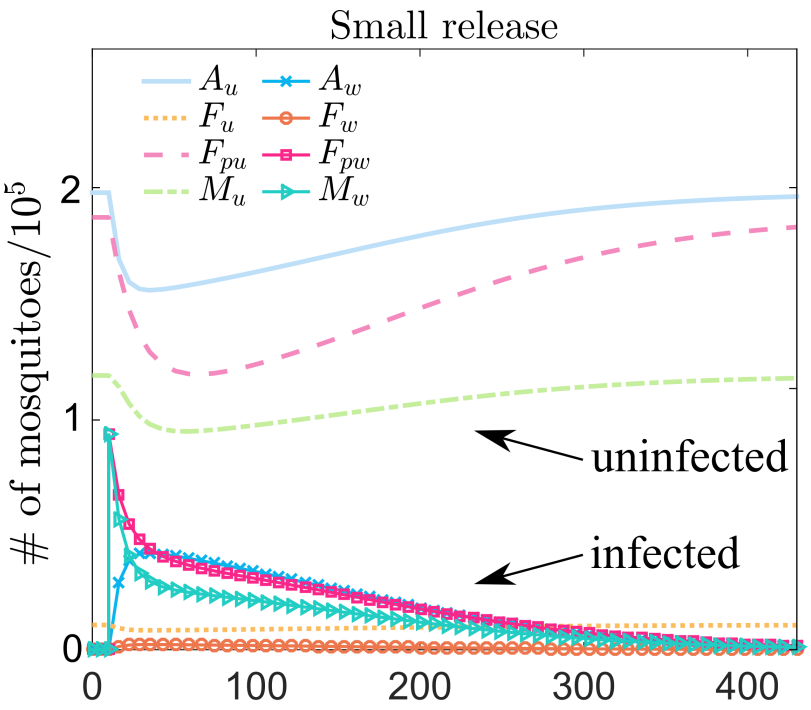
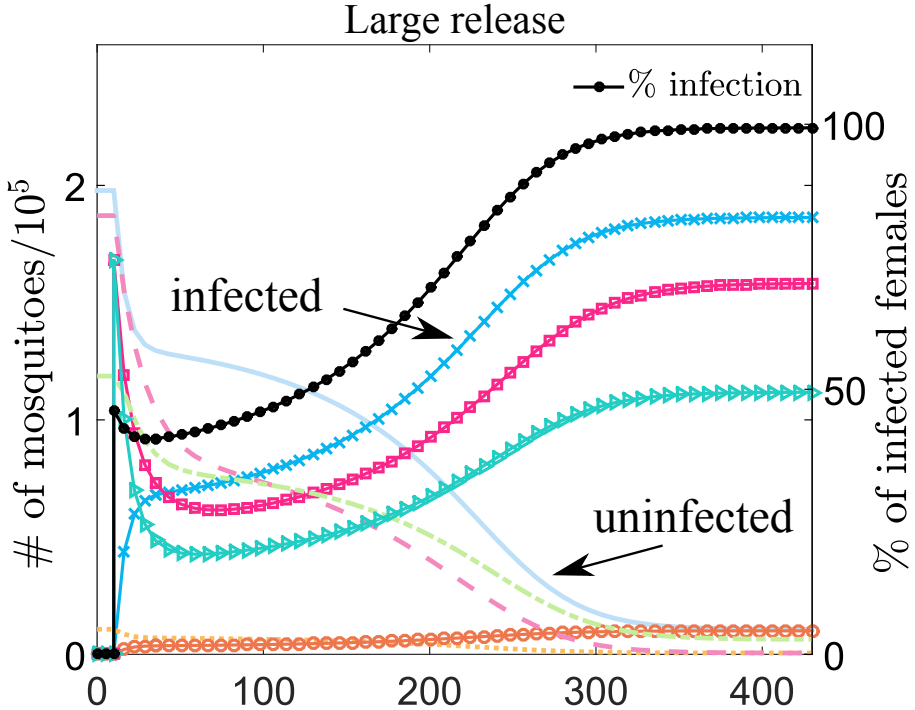


Small release ⇒ infection dies out



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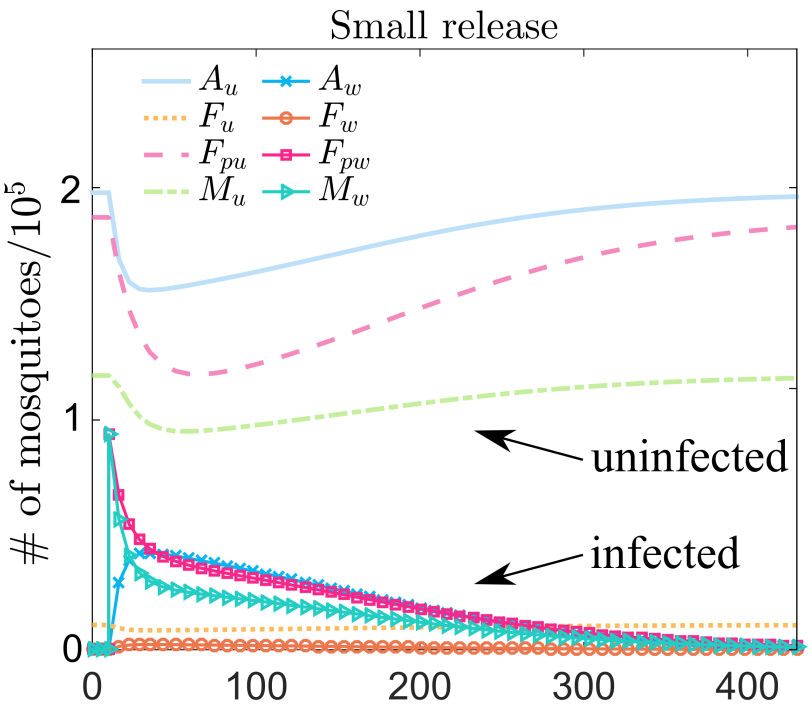

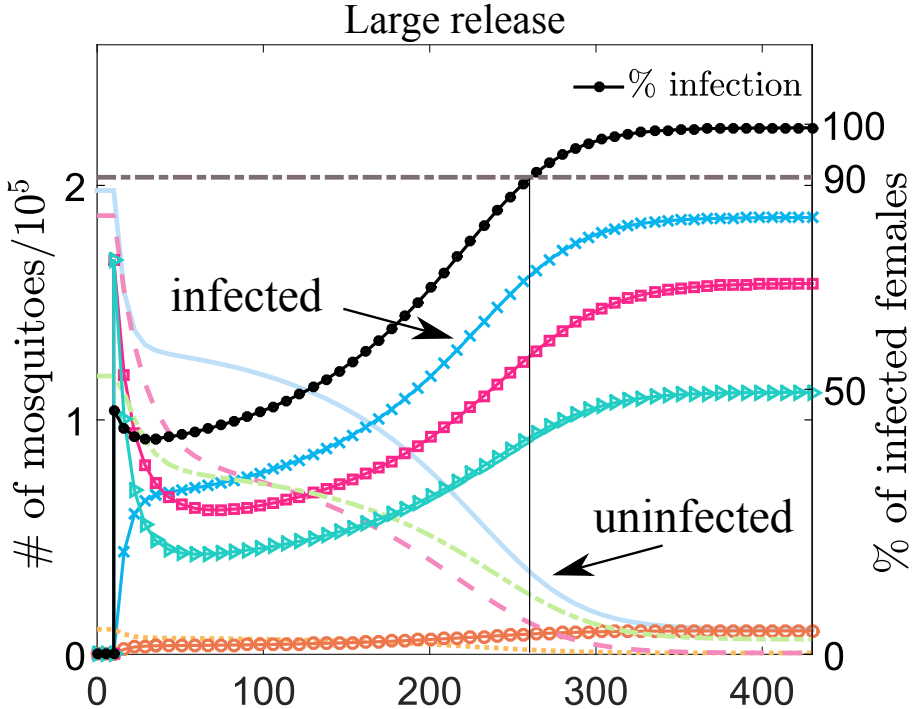

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Large release $\Rightarrow$ infection persists

90% infection is achieved around day 261

left: $0.5X$, right: $0.9X$, threshold: $\approx 0.73X$, $X = F_{pu}^0$

Pre-release mitigation strategies

- threshold condition $\sim$ the fraction of infected mosquitoes

First reduce the number of uninfected mosquitoes (pre-release mitigation)

Then release *Wolbachia*-infected mosquitoes

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Source: United States Agency for International Development (USAID)

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Source: http://entoplp.okstate.edu/mosquito/control/

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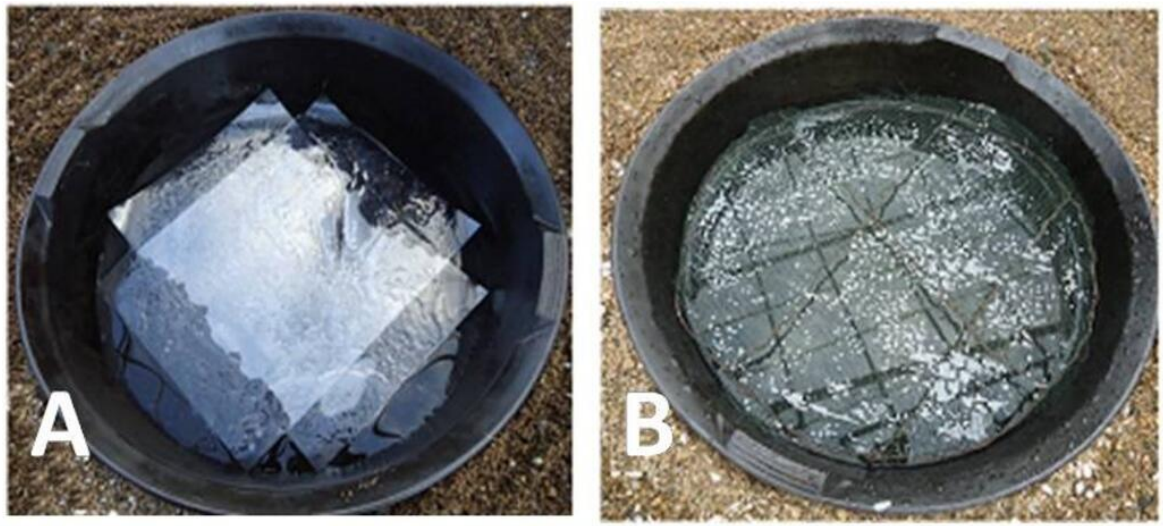

Source: Dugassa, S., Lindh, J.M., Torr, S.J. et al. Malar J (2012) 11: 374.

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Source: http://www.abc.net.au/news/2016-01-07/female-mosquito-wingbeats-trap-males/7073408

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Effectiveness for mosquito control

Approach	Target	Effectiveness
Residual spraying	Adults & larvae	Adults 90%, larvae 40%
Larval control	Aquatic-stage	Eggs 50%, larvae 50%
Sticky ovitrap	Pregnant females	Pregnant females 75%
Acoustic attraction	Males	Males 80%

Integrated mosquito management

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Q3: Release all the infected mosquitoes at once, or repetitively release smaller batches?

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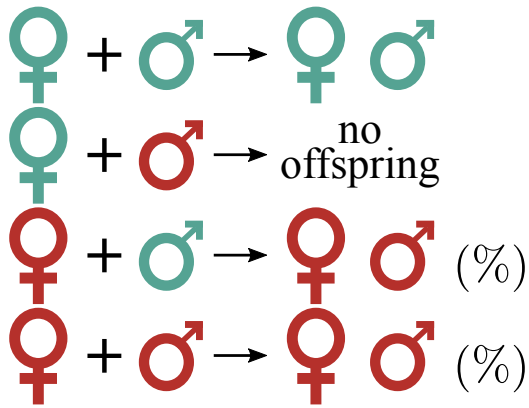

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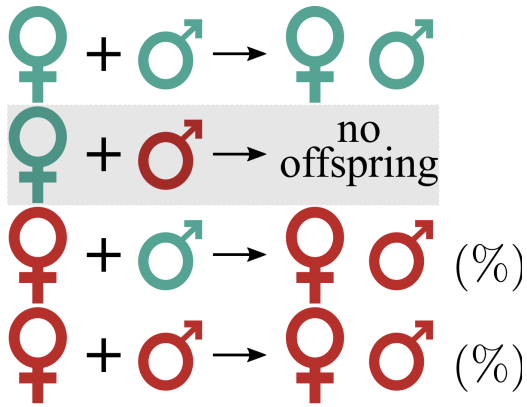

Q1: What is the best mix of infected mosquitoes to release?

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  - $M_w + F_{pw}$ (pregnant)
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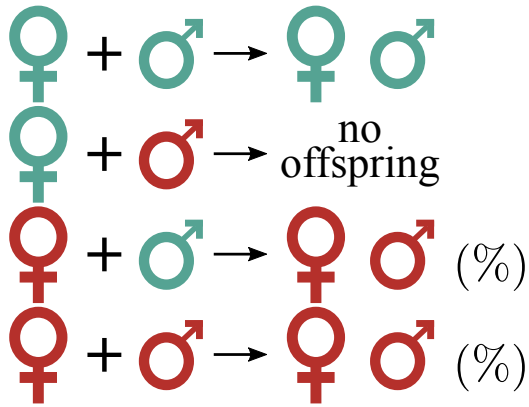

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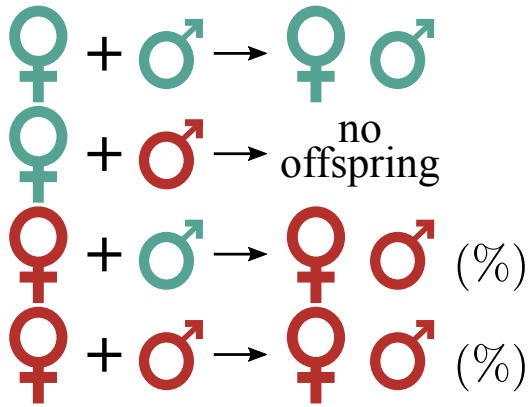

Release Approach	$M_w + F_{pw}$	$M_w + F_w$	
No pre-release mitigation	261	279	days
Residual spraying (F_u, F_{pu}, M_u, A_u)	52	55	days
Larval control (A_u)	203	268	days
Sticky trap (F_{pu})	105	108	days
Acoustic attraction (M_u)	215	227	days

Time (days) to 90% infection in females.

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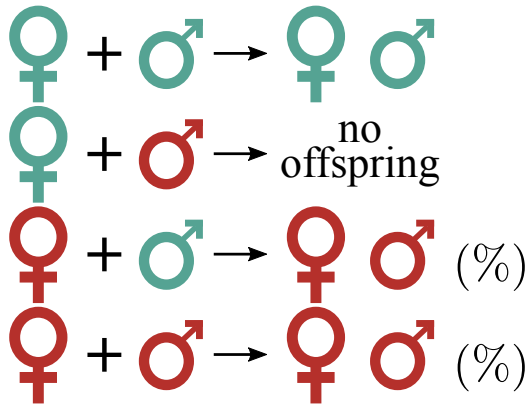

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$\Rightarrow$ residual spraying $>$ sticky trap $>$ larval control $\approx$ acoustic attraction
(F_u, F_{pu}, M_u, A_u) (F_{pu}) (A_u) (M_u)

- remove pregnant females before releasing is the most effective
- remove males does not help a lot
- remove aquatic stage alone without killing pregnant females is not effective

Q3: Is one big release better than split repetitive releases?

- one big release, X females and X males at once
- five smaller releases, $0.2X$ females and $0.2X$ males each

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  - residual spraying: one big release
- constraint from carrying capacity in the aquatic-stage
- efficient use of infected males to sterilized uninfected single females

Outlines

Future work

- may include seasonal variation (temperature, humidity)
  - egg development rate, death rate, carrying capacity of the environment
  - gives more practical guide when the releasing process spans more than one season
- may include spatial heterogeneity
  - for real field releases, the infected population is released at several distant spots
  - the infection diffuses out in a radial symmetric manner

Acknowledgment

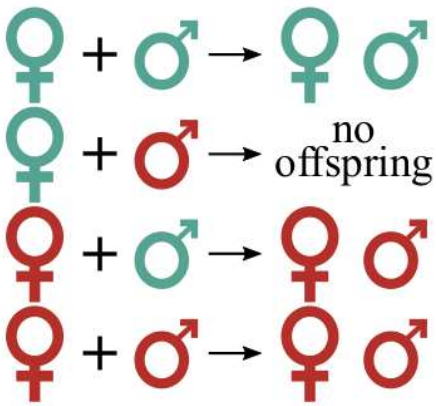
- James (Mac) Hyman, Mathematics Department, Tulane
- Dawn Wesson, Panpim Thongsripong, Department of Tropical Medicine, Tulane
- Patricia Scaraffia, Department of Tropical Medicine, Tulane

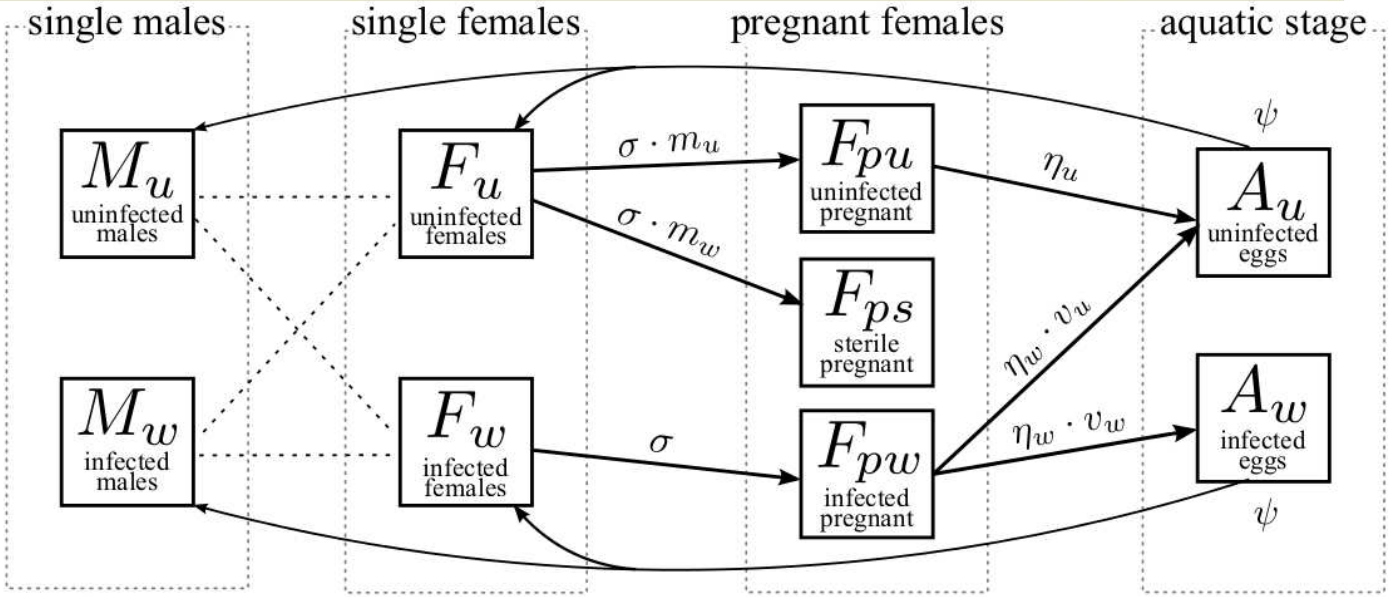
This research was partially supported by

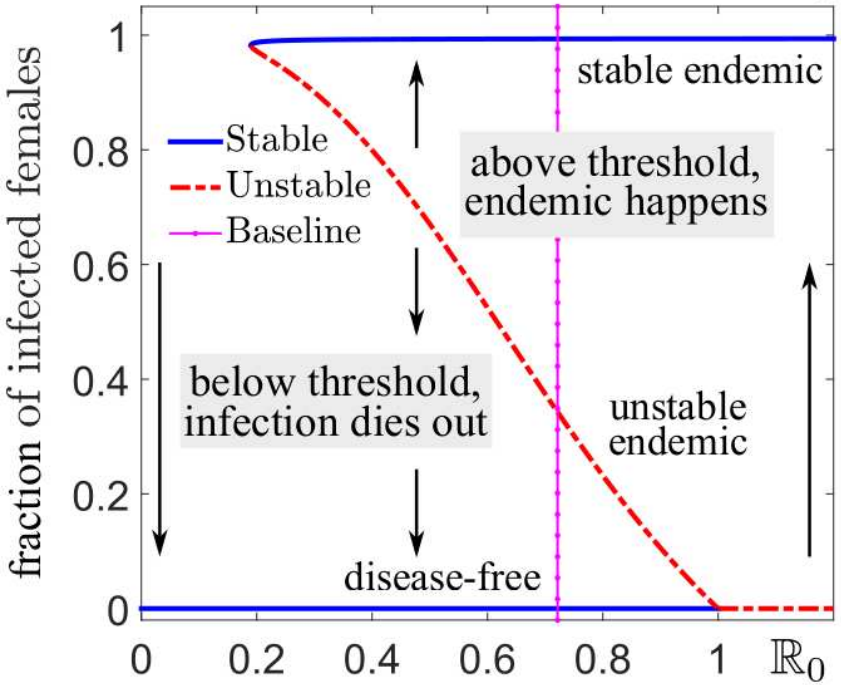
- NSF/MPS/DMS-NIH/NIGMS award
- NIH-NIGMS Models of Infectious Disease Agent Study (MIDAS) award

Thank you!

Create a stable *Wolbachia* epidemic in wild moquito population







- two-sex transmission
- multi-stage female life cycle
- carrying capacity for aquatic stage

$$\mathbb{R}_0 = \frac{\#\text{ of new infected eggs per infected egg}}{\#\text{ of new uninfected eggs per uninfected egg}}$$

$$\text{threshold} = \frac{\#\text{ of infected eggs}}{\#\text{ of uninfected eggs}}$$

Baseline parameter values and ranges

	Description	Baseline	Range
b_f	Female birth probability	0.5	0.50 – 0.57
b_m	Male birth probability $= 1 - b_f$	0.5	0.43 – 0.50
σ	Per capita mating rate	1	-
ϕ_u	Per capita egg F_{pu} laying rate	13	12 – 18
ϕ_w	Per capita egg F_{pw} laying rate	11	8 – 12
v_w	Maternal transmission efficiency	0.95	0.89 – 1
ψ	Per capita development rate	1/8.75	1/9.2 – 1/8.1
μ_a	Death rate for A_u or A_w	0.02	0.01 – 0.04
μ_{fu}	Death rate for F_u	1/17.5	1/21 – 1/14
μ_{fw}	Death rate for F_w	1/15.8	1/19 – 1/12.6
μ_{mu}	Death rate for M_u	1/10.5	1/14 – 1/7
μ_{mw}	Death rate for M_w	1/10.5	1/14 – 1/7
K_a	Carrying capacity of A_u or A_w	2×10^5	-

Full table for Q3:

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- constraint of carrying capacity in the aquatic-stage
- efficient use of male to sterilize uninfected single females

- sticky trap $\approx$ spraying: create a big gap in the aquatic-stage, fill the gap ASAP
- acoustic attraction: get rid of redundant males $\approx$ no mitigation
- larval control: big delay, b/c not fill in the gap in time $\rightarrow$ no mitigation

Safety concerns of a *Wolbachia*-based strategy?

- it can be transferred to humans through the bites?
  - *Wolbachia* are naturally found in a large range of insect species
  - *Wolbachia* have never been found in humans or other mammals, e.g. birds, reptiles or fish
- it be transferred to other organisms?
  - *Wolbachia* is not infectious, only vertically transmitted
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- potential consequences over a long-term period and large geographic scale?
- evolution of the virus in response to the presence of *Wolbachia*?

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