Modeling sustained transmission of Wolbachia among *Anopheles* mosquitoes: Implications for Malaria control in Haiti

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Introduction

- Plasmodium facliparum is a parasitic disease spread by the bite of an infected female *Anopheles* mosquito, which the specific species is known for causing *falciparum malaria*
- The bacteria *Wolbachia pipientis* is widespread among arthropods and there are ongoing trials for sustaining wild populations of *Wolbachia*-infected *Aedes aegypti* mosquitoes to prevent the spread of abroviruses, such as Zika, Chikingunya, and Dengue fever

Female anopheles moquito, Scientists Against Malaria

Mechanics of Wolbachia

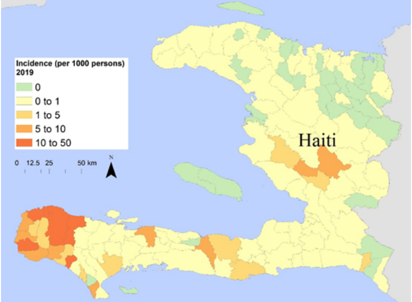
- Malaria elimination is possible in Haiti through Wolbachia release. Preliminary studies of *Anopheles (An.)* mosquitoes infected with *wAlbB Wolbachia* bacteria show that infected mosquitoes are less capable of spreading Malaria
- Infection induces a cytoplasmic incompatibility that disrupts the infection cycle through population suppression, inhibiting within-vector replication of the *Plasmodium falciparum* parasite, and reducing vector competence
- Vectors are rendered essentially infertile due to cytoplasmic incompatibility

Importance of Wolbachia

- Our issue is of public health importance due the high mortality associated with falciparum malaria - therefore new and novel vector control strategies should be explored to reduce mosquito populations
- The bacteria *Wolbachia pipientis* is widespread among arthropods and there are ongoing trials for sustaining wild populations of *Wolbachia*-infected *Aedes aegypti* mosquitoes to prevent the spread of abroviruses, such as Zika, Chikingunya, and Dengue fever
- By employing various release strategies, *Wolbachia* can be used as an effective mitigation strategy for the spread of malaria

Geographic Scope

- Release of *Wolbachia*-infected mosquitoes as a control measure in this setting is both feasible and appropriate
- The scope of our model is therefore limited to a country in an elimination phase, characterized by highly focalized and seasonal malaria transmission, such as Haiti



Spatial distribution of malaria in Haiti

Objective

- Our objective is therefore to create and analyze a model to evaluate different approaches for **maintaining *wAlbB* infection within *Anopheles albimanus* mosquitoes** and apply it to assess its potential as a malaria control strategy in Haiti
- We will evaluate the **number of days required to reach endemic, stable *wAlbB* transmission (**90%**)** among a wild-type *An. albimanus* mosquito population, for each release scenario- measured as ratio of type of mosquitoes released and timing of mosquitoes released, while accounting for pre-existing vector control baseline interventions.

Method

- We assemble a system of 9 ordinary non-linear differential equations
- Vertical transmission is exhibited in our model, indicating that Wolbachia infection is transmitted primarily from infected female mosquitoes to their offspring
- Through numerical simulation, we can find the most effective release strategy (the shortest amount of time to reach 905 infection)
- The model divides the population based on the mosquito's sex, infection status, pregnancy status, and includes and aquatic stage.
- We change input model parameter values to be *Anopheles*-specific (based off in-depth literature review)

Assumptions

With any model for infectious disease, a list of assumptions is presented to outline both the efficacy and shortcomings of the model

1. Perfect vertical transmission (100%) of *Wolbachia*, i.e. from infected female mosquitoes to offspring for one strain (wAlbB)
2. The aquatic state represents all development stages (egg, larva, pupa) of the mosquito life cycle
3. We use homogeneous birth rates, lifespan of aquatic stages and egg laying rates across sexes and infectivity status (*Wolbachia*-free and *Wolbachia*-infected mosquitoes)
4. Our model uses parameters relative to the rainy season at this time
5. The implemented carrying capacity will remain constant during the time we evaluate one season and it is not dependent on time
6. The model accounts for vector control interventions such as insecticide-treated nets (ITNs) and indoor residual spraying (IRS), however does not account for other vector control strategies

Compartments of Model

Notation	**Description**
A_u	Uninfected mosquito eggs, pupae and larvae
A_w	Infected mosquito eggs, pupae and larvae
F_u	Uninfected adult female mosquitoes
F_w	Infected adult female mosquitoes
F_{pu}	Uninfected adult pregnant female mosquitoes
F_{pw}	Infected adult pregnant female mosquitoes
F_{ps}	Adult sterile female mosquitoes
M_u	Uninfected adult male mosquitoes
M_w	Infected adult male mosquitoes

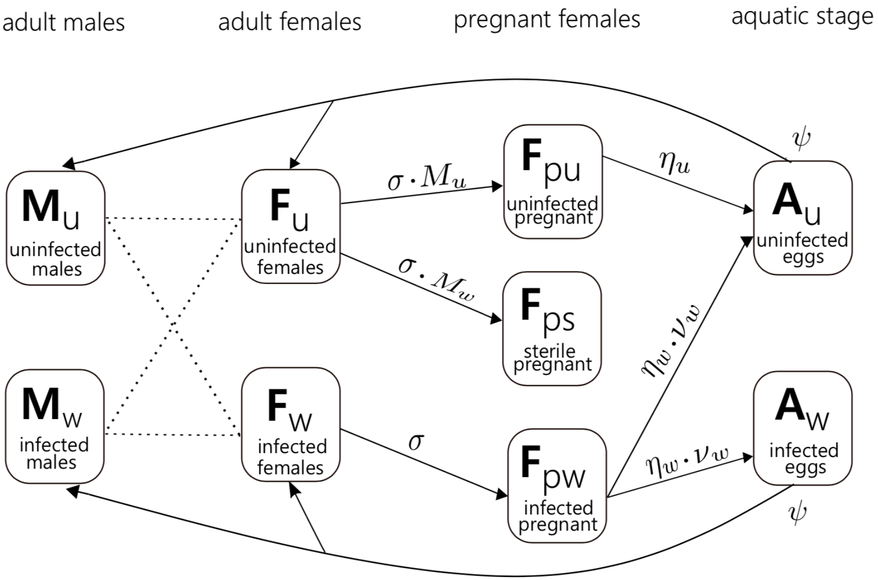
Description of Compartments

1. Male and female mosquito compartments
    - Male mosquitoes are uninfected (denoted as M_u) or infected (M_w), and female mosquitoes are either uninfected (F_u) or infected (F_w)
    - Females enter the pregnant stage after mating with males at a rate of σ
    - Fraction of uninfected and infected males are defined as m_u and m_w, respectively
2. Pregnant female compartments
    - Depending on infection status of male mosquitoes, female mosquitoes can be pregnant and uninfected (F_{pu}), pregnant yet sterile (F_{ps}) or infected pregnant (F_{pw})
    - Only pregnant sterile females do not produce offspring

Description of Compartments (cont.)

1. Pregnant females produce aquatic-stage mosquitoes:
   - Uninfected pregnant females (F_{pu}) produce uninfected eggs (A_u) at rate η_u
   - Infected pregnant females (F_{pw}) produce infected offspring (A_w) at rate η_w
   - perfect maternal transmission, V_w (no arrow with V_u in diagram)
   - Eggs laying rates are denoted as η_u and η_w for F_{pu} and F_{pw}, respectively
   - Aquatic-stage mosquitoes hatch and develop into adult mosquitoes at rate ψ
   - As previously mentioned, the aquatic stage encompasses egg hatching (2-3 days) and development of larvae ($\approx$7 days) and pupae (2-3 days)

Flow of Transmission



Full Parameter Table

Notation	Description	Dimension	Value	Range	Citation
	Independent Model Parameters, *Anopheles*-specific				
σ	Per capita mating rate	$PT^{-1}F^{-1}$	1	-	[3]
b_f	Female mosquito birth rate	–	0.5	-	[4]
b_m	Male mosquito birth rate	–	0.5	-	[4]
ϕ_u	F_{pu} Per capita egg laying rate	$AT^{-1}P^{-1}$	1/3.1	-	[3]
ϕ_w	F_{pw} Per capita egg laying rate	$AT^{-1}P^{-1}$	1/3.1	-	[3]
v_w	*wAlbB* maternal transmission rate (females to eggs)	–	1	0.95-1	[1]
v_u	Infection leakage rate (no maternal transmission)	–	0	0- 0.05	[1]
ψ	Hatching rate (emergence time) for aquatic-state mosquitoes	$A^{-1}T^{-1}N$	1/10	1/9.45 - 1/10.2	[3]
μ_{au}	Average lifespan for uninfected aquatic stages. $= 1/\tau_{au}$	T^{-1}	1/27	-	[3]
μ_{aw}	Average lifespan for infected aquatic stages. $= 1/\tau_{aw}$	T^{-1}	1/10	-	[3]
μ_{fpu}	Average lifespan for uninfected pregnant female mosquitoes. $= 1/\tau_{fpu}$	T^{-1}	1/16	-	[3]
μ_{fu}	Average lifespan for uninfected single female mosquitoes. $=1/\tau_{fu}$	T^{-1}	1/16	-	[3]
μ_{fpw}	Average lifespan for infected pregnant female mosquitoes. $=1/\tau_{fpw}$	T^{-1}	1/16	-	[3]
μ_{fw}	Average lifespan of infected single female mosquitoes. $= 1/\tau_{fw}$	T^{-1}	1/16	-	[3]
μ_{mu}	Average lifespan of uninfected adult male mosquitoes. $= 1/\tau_{mu}$	T^{-1}	1/16	-	[3]
μ_{mw}	Average lifespan infected adult male mosquitoes. $= 1/\tau_{mw}$	T^{-1}	1/16	-	[3]
ν_v	Average incubation time for mosquitoes	T			
K_a	Regional carrying capacity of aquatic stages	–	$2 * 10^5$	-	[4]
	Dependent Model Parameters				
$m_u(t)$	Fraction of adult male mosquitoes that are uninfected $= M_u/(M_u + M_w)$	–	N/A	N/A	N/A
$m_w(t)$	Fraction of adult male mosquitoes that are infected $= M_w/(M_u + M_w)$	–	N/A	N/A	N/A
$\eta_u(t)$	F_{pu} egg laying rate for $\eta_u = \phi_u[1 - (A_u + A_w)/K_a]$	$PA^{-1}T^{-1}$	N/A	N/A	
$\eta_w(t)$	F_{pw} egg laying rate $\eta_w = \phi_w[1 - (A_u + A_w)/(K_)]$	$PA^{-1}T^{-1}$	N/A	N/A	N/A

System of Differential Equations (Infected)

$$\frac{dA_w}{dt} = \nu_w \eta_w F_{pw} - (\mu_{aw} + \psi) A_w, \tag{1a}$$

$$\frac{dF_w}{dt} = b_f \psi A_w - (\sigma + \mu_{fpu}) F_w, \tag{1b}$$

$$\frac{dF_{pw}}{dt} = \sigma F_w - \mu_{fpw} F_{pw}, \tag{1c}$$

$$\frac{dM_w}{dt} = b_m \psi A_w - \mu_{mw} M_w. \tag{1d}$$

- The flow of transmission of the infected equations is as shown above
- Mosquito infection is transmitted exclusively from infected pregnant females

System of Differential Equations (Uninfected)

$$\frac{dA_u}{dt} = \eta_u F_{pu} + \nu_u \eta_w F_{pw} - (\mu_{au} + \psi) A_u, \tag{2a}$$
$$\frac{dF_u}{dt} = b_f \psi A_u - (\sigma + \mu_{fu}) F_u, \tag{2b}$$
$$\frac{dF_{pu}}{dt} = \sigma m_u F_u - \mu_{fu} F_{pu}, \tag{2c}$$
$$\frac{dM_u}{dt} = b_m \psi A_u - \mu_{mu} M_u, \tag{2d}$$
$$\frac{dF_{ps}}{dt} = \sigma m_w F_u - \mu_{fu} \mu_{fpu} F_{ps}. \tag{2e}$$

- Females are sterilized by infected male mosquitoes
- The death of sterile females is at a joint rate between the death of uninfected non-pregnant and uninfected pregnant

Diagnostic Equations

- Diagnostic equations often follow a system of differential equations, to fill in some of the finer details of the model
- The first set of diagnostics is used to track total general infected, and uninfected populations, respectively:

$$N_{tot} = A_u + A_w + F_u + F_w + F_{pu} + F_{pw} + F_{ps} + M_u + M_w, \tag{3a}$$
$$N_w = A_w + F_w + F_{pw} + M_w, \tag{3b}$$
$$N_u = A_u + F_u + F_{pu} + F_{ps} + M_u. \tag{3c}$$

- The next set show the fraction of male uninfected, and infected populations, respectively:

$$m_u(M_u, M_w) = \frac{M_u}{(M_u + M_w)}, \tag{4a}$$
$$m_w(M_u, M_w) = \frac{M_w}{(M_u + M_w)}. \tag{4b}$$

Basic Reproductive Number

- The basic reproductive number of an epidemic model, most commonly denoted as $\mathbb{R}_0$, is the amount of secondary infection that one infected vector produces
- For example, if one person is infected and the basic reproductive number is 2, then that person will infect two people
- There are two approaches to calculate the reproductive number
- In the following slides, the reproductive number is calculated using mathematical intuition, and then it is calculated using the Next-Generation-Matrix approach

Basic Reproductive Number, Intuitive Approach (cont.)

- To find the basic reproductive number intuitively, we introduce two dimensionless **G-factors**, denoted $\mathbb{G}_{0_u}$ and $\mathbb{G}_{0_w}$, which calculates the average amount of eggs that the female will produce in its lifetime
- We begin by finding the probability that an uninfected egg hatches into the female uninfected compartment:

$$\frac{b_f \psi}{\mu_{au} + \psi} \tag{5}$$

- To proceed, we find the probability of the uninfected female non-pregnant mosquito transitions to the pregnant compartment:

$$\frac{\sigma}{\sigma + \mu_{fpu}} \tag{6}$$

- We then determine the amount of uninfected eggs that the uninfected pregnant female lays in its life cycle:

$$\frac{\phi_u}{\mu_{fpu}} \tag{7}$$

Basic Reproductive Number, Intuitive Approach (cont.)

- By finding the joint probability of each compartment transition multiplied by the amount of eggs lay, the uninfected G-factor is:

$$\mathbb{G}_{0u} = \left(\frac{b_f\psi}{\mu_{a_u} + \psi}\right)\left(\frac{\sigma}{\sigma + \mu_{fu}}\right)\left(\frac{\phi_u}{\mu_{fu}}\right) \tag{8}$$

- An identical approach is taken to the infected G-factor, so the work is omitted
- The G-factor for the infected compartment is as follows:

$$\mathbb{G}_{0w} = \left(\frac{b_f\psi}{\mu_{a_w} + \psi}\right)\left(\frac{\sigma}{\sigma + \mu_{fw}}\right)\left(\frac{\phi_w}{\mu_{fw}}\right) \tag{9}$$

Basic Reproductive Number

- By approaching these two factors intuitively, the basic reproductive number can be found by taking the ratio of $\mathbb{G}_{0w}$ and $\mathbb{G}_{0u}$:

$$\mathbb{R}_0 = \mathbb{G}_{0w}/\mathbb{G}_{0u} = \left(\frac{b_f\psi}{\mu_{a_u}+\psi}\right)\left(\frac{\sigma}{\sigma+\mu_{fu}}\right)\left(\frac{\phi_u}{\mu_{fu}}\right)\Big/\left(\frac{b_f\psi}{\mu_{a_w}+\psi}\right)\left(\frac{\sigma}{\sigma+\mu_{fw}}\right)\left(\frac{\phi_w}{\mu_{fw}}\right) \tag{10}$$

- The ratio of infected eggs lay to uninfected eggs lay is the basic reproductive number
- This is intuitively correct as if $\mathbb{R}_0 > 1$, there will be more infected eggs per uninfected egg lay, and the infection will spiral unstably
- Conversely, if $\mathbb{R}_0 < 1$, the ratio is driven by uninfected eggs and infection will die out

Basic Reproductive Number, NGM Approach

- The "next-generation-matrix" approach is often crucial in epidemic models, as it can precisely calculate the basic reproductive number
- To begin, we denote a single dimension matrix:

$$\mathbf{X} = (A_w, F_w, F_{pw}, M_w)^T \tag{11}$$

- By taking the time derivative of this matrix and subtracting the infection that leaves the system from the infection that enters the system, we get:

$$\frac{dX}{dt} = \begin{pmatrix} A_w \\ F_w \\ F_{pw} \\ M_w \end{pmatrix} = \begin{pmatrix} v_w \eta_w F_{pw} \\ 0 \\ 0 \\ 0 \end{pmatrix} - \begin{pmatrix} (\mu_{a_w} + \psi) A_w \\ -b_f \psi A_w + (\sigma + \mu_{f_w}) F_w \\ -\sigma F_w + \mu_{f_w} F_{pw} \\ -b_m \psi A_w + \mu_{mw} M_w \end{pmatrix} = F(X) - V(X) \tag{12}$$

Basic Reproductive Number, NGM Approach (cont.)

- Now that we have each matrix, we proceed by taking the Jacobian of both F and V, with respect to X. Each matrix is yield by:

$$J_f = \frac{dF}{dX} = \begin{pmatrix} 0 & 0 & v_w \eta_w & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{13}$$

$$and \tag{14}$$

$$J_v = \frac{dV}{dX} = \begin{pmatrix} \mu_{a_w} + \psi & 0 & 0 & 0 \\ -b_f \psi & \sigma + \mu_{f_w} & 0 & 0 \\ 0 & -\sigma & \mu_{f_w} & 0 \\ -b_m \psi & 0 & 0 & \mu_{mw} \end{pmatrix} \tag{15}$$

- Now, in order to find R_0, we must calculate the spectral radius, or maximum Eigenvalue, of $J_f J_v^{-1}$. To calculate $J_v^{-}1$ we use a 4x4 inverse matrix calculator. This yields:

$$J_v^{-1} = \begin{pmatrix} \frac{1}{\mu_{a_w}+\psi} & 0 & 0 & 0 \\ \frac{b_f\psi}{(\sigma+\mu_{fw})(\mu_a+\psi)} & \frac{1}{\sigma+\mu_{fw}} & 0 & 0 \\ \frac{b_f\psi\sigma}{\mu_{fw}(\sigma+\mu_{fw})(\mu_a+\psi)} & \frac{\sigma}{\mu_{fw}(\sigma+\mu_{fw})} & \frac{1}{\mu_{fw}} & 0 \\ \frac{b_m\psi}{\mu_{mw}(\mu_a+\psi)} & 0 & 0 & \frac{1}{\mu_{mw}} \end{pmatrix} \tag{16}$$

- Upon multiplying the two matrices and taking the limit [A-λI], we get the basic reproductive number:

$$\mathbb{R}_0 = \left(\frac{\psi}{\mu_{a_u}+\psi}\right)\left(\frac{\sigma}{\sigma+\mu_{fu}}\right)\left(\frac{\phi_u}{\mu_{fu}}\right)\Bigg/\left(\frac{\psi}{\mu_{a_w}+\psi}\right)\left(\frac{\sigma}{\sigma+\mu_{fw}}\right)\left(\frac{\phi_w}{\mu_{fw}}\right) \tag{17}$$

Disease Free Equilibrium

- The disease-free equilibrium is defined as the equilibrium point at which no disease is present in the population.

Procedure: Let $DFE = (A_u^0, A_w^0, F_u^0, F_w^0, F_{pu}^0, F_{pw}^0, M_u^0, M_w^0)$ denote the disease-free equilibrium point of our system (1a)-(1i), which can be found by setting all the infected compartments equal to zero $A_w = F_w = F_{pw} = M_w = 0$. The solution will be given by

$$A_u^0 = K_a\left(1 - \frac{1}{\mathbb{G}_{0u}}\right),$$

$$F_u^0 = \frac{b_f\psi}{\mu_{fu} + \sigma}A_u^0,$$

$$F_{pu}^0 = \frac{b_f\psi\sigma}{(\mu_{fu} + \sigma)\mu_{fu}}A_u^0,$$

$$M_u^0 = \frac{b_m\psi}{\mu_{mu}}A_u^0,$$

$$A_w^0 = F_w^0 = F_{pw}^0 = M_w^0 = 0.$$

Complete Infection Equilibrium

- The maternal transmission ν_w represents the rate at which the infected pregnant females produce infected offspring.
- **Procedure:** to find the CIE, where all the mosquitoes are infected, we set all the uninfected compartments equation to zero $A_u = F_u = F_{pu} = M_u = 0$ in the system (1a)-(1i), assuming perfect maternal transmission $\nu_w = 1$.

Let $CIE = (A_u^c, A_w^c, F_u^c, F_w^c, F_{pu}^c, F_{pw}^c, M_u^c, M_w^c)$ denote the complete-free equilibrium point, where

$$A_w^c = K_a\left(1 - \frac{1}{\mathbb{G}_{0w}}\right)$$

$$F_w^c = \frac{b_f\psi}{\mu_{fw} + \sigma}A_w^0$$

$$F_{pw}^c = \frac{b_f\psi\sigma}{(\mu_{fw} + \sigma)\mu_{fw}}A_w^0$$

$$M_w^c = \frac{b_m\psi}{\mu_{mw}}A_w^0$$

Numerical Simulations

- **There are 3 mosquito release scenarios that we employ to study the amount of time it takes to reach stable infection**

1. Release of infected pregnant females (F_{pw}) and infected males (M_w)
2. Release of infected, non-pregnant females (F_w) and infected males (M_w)
3. Release of pregnant females only (F_{pw})

- **Additionally there are 3 scenarios in which interventions are or not used**:

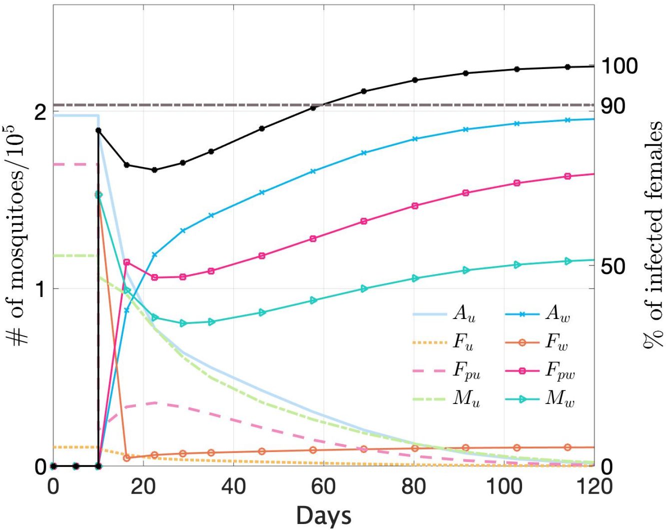
1. No intervention
2. Insecticide Treated Nets (ITN's)
3. Indoor Residual Spreading (IRS's)

Results

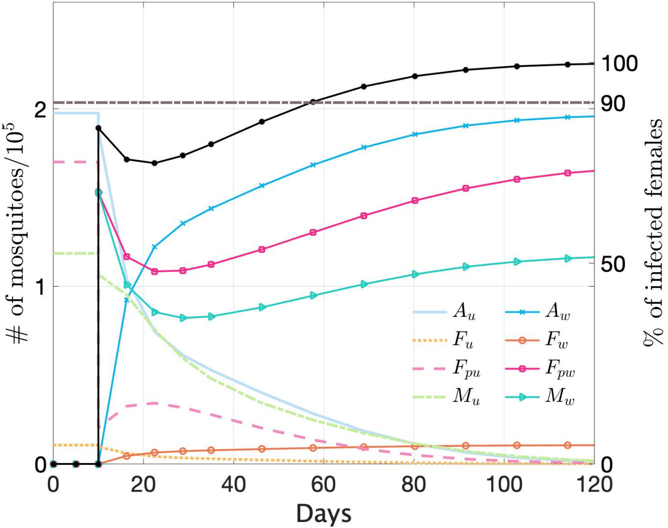
Release Scenario	ITN	IRS	No intervention
F_{pw} and M_w	79.6	**63.2**	0
F_w and M_w	81.4	**64.7**	0
Only F_{pw}	98.5	**82.1**	0

- This table illustrates the results of the numerical simulation
- Applying no outside intervention is useless to sustaining Wolbachia infection, as the time to reach endemic infection is not achieved in a reasonable amount of time
- **The most effective combination is torelease pregnant female mosquitoes (F_{pw}), and adult male mosquitoes (M_w), in tandem with Indoor Residual Spraying with a time to reach endemic infection at 63.2 days**

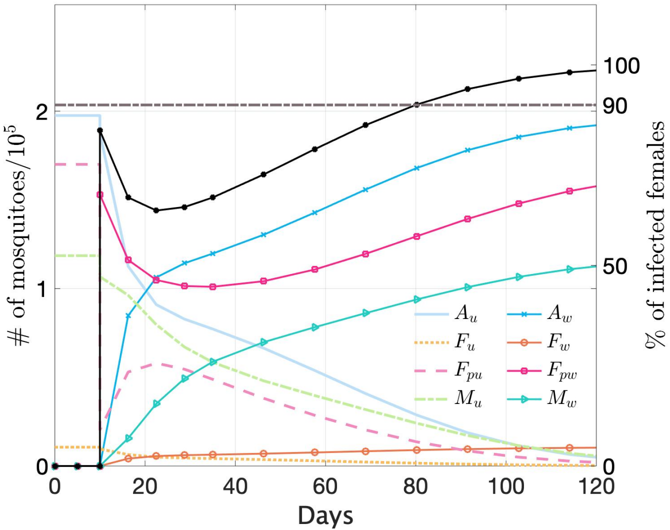
Results (IRS, F_{pw} and M_w)



Results (IRS, F_w and M_w)



Results (IRS, only F_{pw})



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