

# Evaluating the long-term effectiveness of imperfect *Wolbachia* interventions in preventing arboviral disease: the potential role of immune dynamics

## Background

- *Wolbachia* (wMel)-infected *Aedes aegypti* were released in Rio de Janeiro, Brazil from 2017-2021 (Fig 1A-C).
- The intervention led to variable dengue risk reduction over time and was not significantly protective during epidemic transmission in 2024 (Fig 1D).
- To explore mechanisms underlying variations in effectiveness, we simulated dengue dynamics following wMel introduction.

## Methods

- We simulated dengue transmission using a coupled human SEIR and mosquito SEI framework (Fig 2).
- wMel introduction was modeled as a reduction in effective wildtype (infectious) mosquitoes (assuming wMel-infected mosquitoes are not infectious).
- We tested varying baseline mosquito abundance, introgression level, and immunity scenarios.
- We estimated intervention effects comparing simulated incidence at an introgression level against an otherwise identical simulation with 0% introgression.

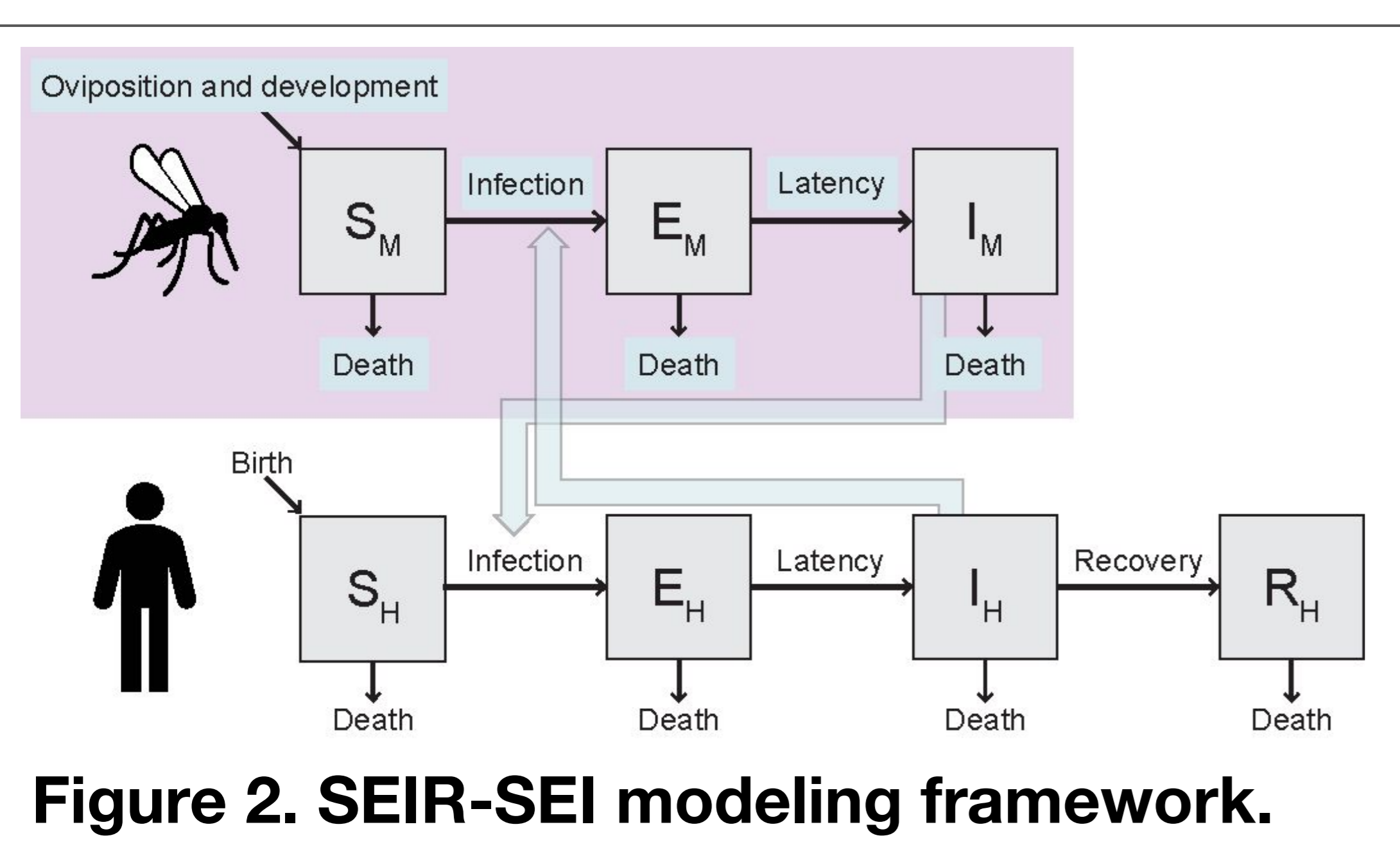


Figure 2. SEIR-SEI modeling framework.

## Results

- Simulations show larger incidence reductions in populations near endemic equilibrium susceptibility compared to highly susceptible populations (Fig 3).
- Yearly incidence can be transiently higher with wMel introduction than without, as large outbreaks deplete susceptibles in no-intervention scenarios while transmission continues for longer under partial wMel introgression.
- Cumulative incidence is always lower after wMel introduction regardless of introgression level.

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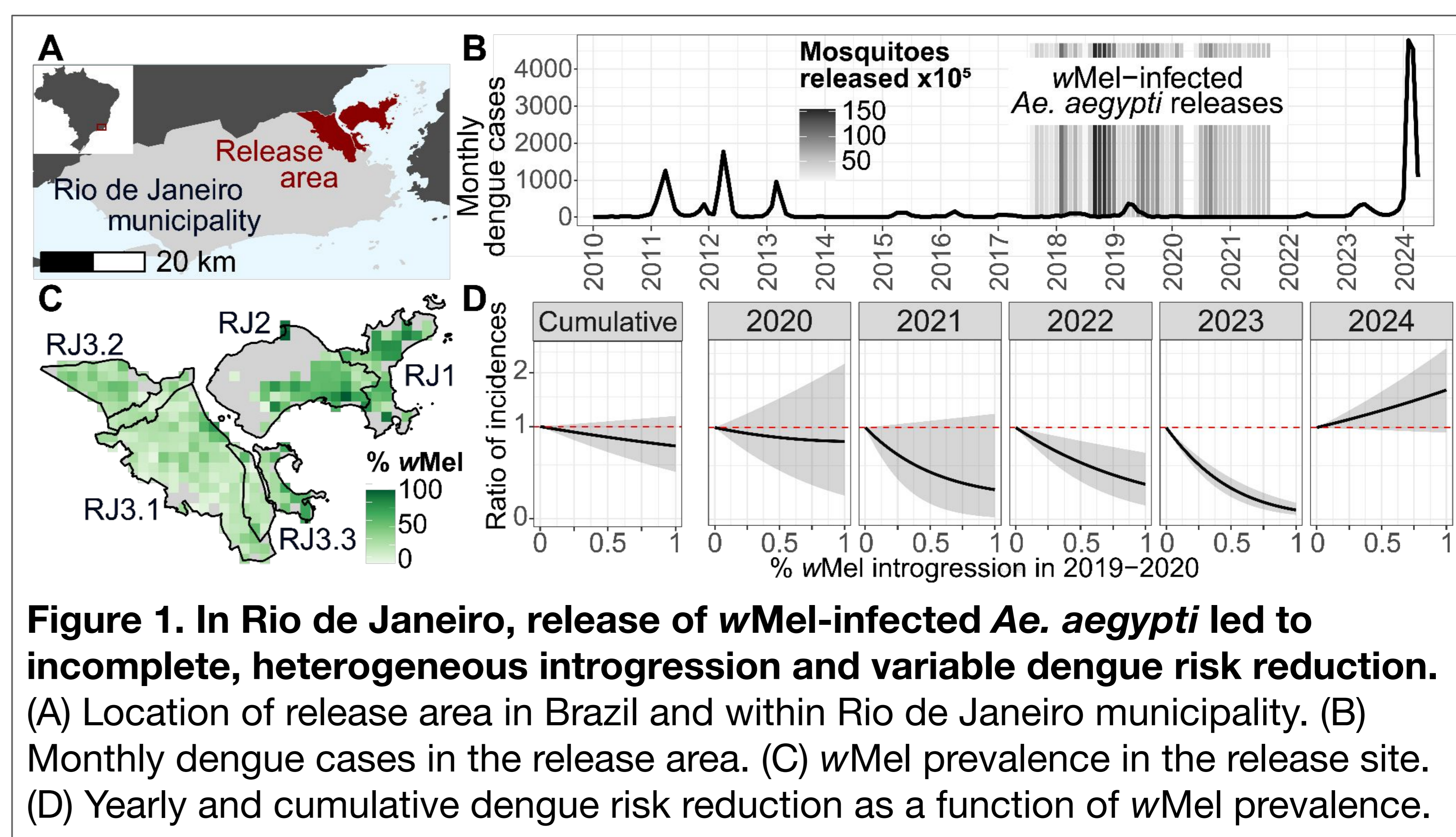


Figure 1. In Rio de Janeiro, release of wMel-infected *Ae. aegypti* led to incomplete, heterogeneous introgression and variable dengue risk reduction. (A) Location of release area in Brazil and within Rio de Janeiro municipality. (B) Monthly dengue cases in the release area. (C) wMel prevalence in the release site. (D) Yearly and cumulative dengue risk reduction as a function of wMel prevalence.

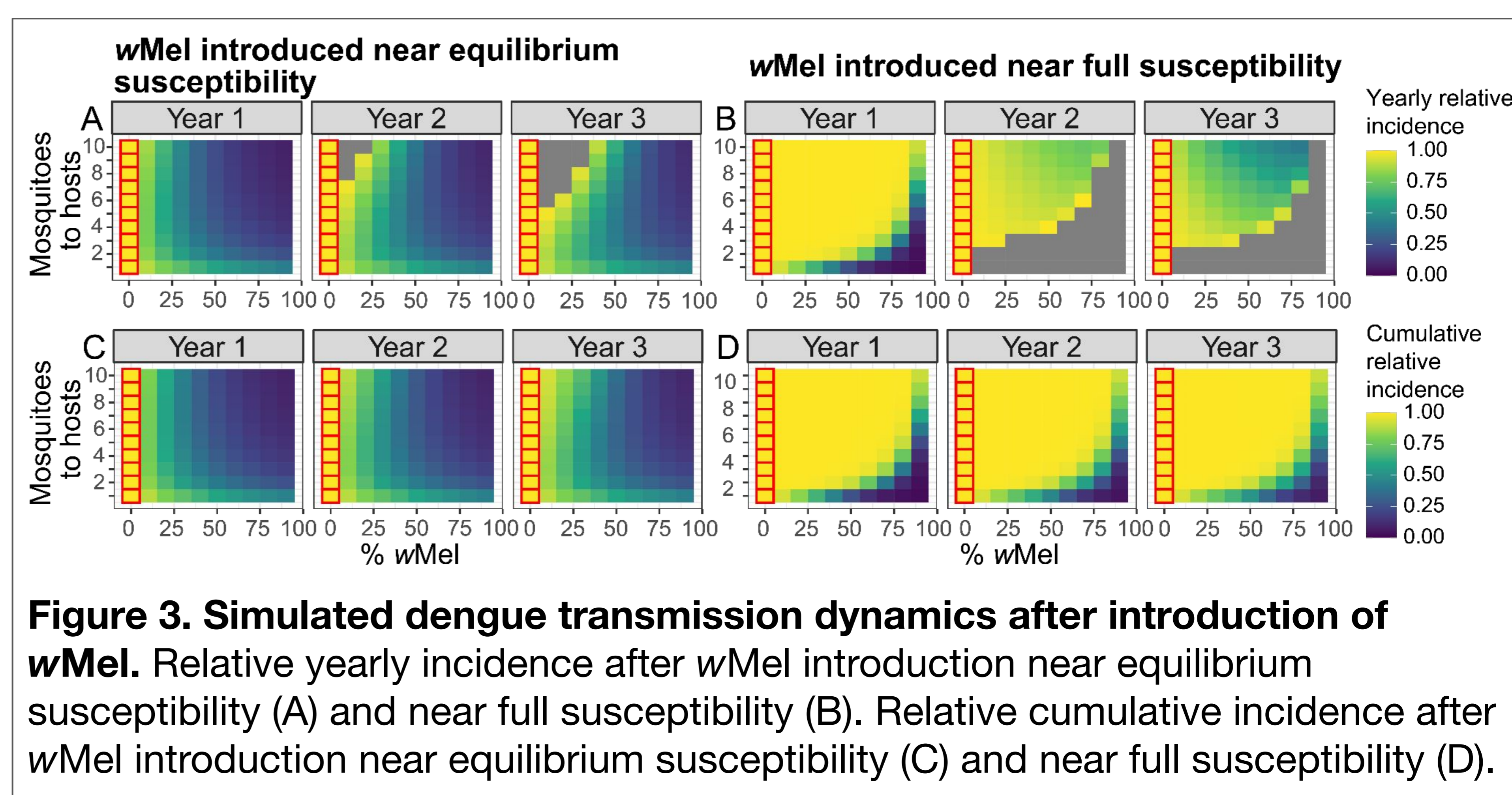


Figure 3. Simulated dengue transmission dynamics after introduction of wMel. Relative yearly incidence after wMel introduction near equilibrium susceptibility (A) and near full susceptibility (B). Relative cumulative incidence after wMel introduction near equilibrium susceptibility (C) and near full susceptibility (D).

## Key conclusions

- wMel effectiveness is context-dependent; more modest effects may be observed in settings with high susceptibility, incomplete introgression, or high spatial heterogeneity in transmission risk.
- Use of cumulative incidence metrics, longer observation periods and addressing time-varying confounding and effect modification by population immunity may be needed to more accurately measure intervention effects in these settings.
- Effectiveness measured in areas long endemic to dengue will typically be larger than areas where dengue experiences first large outbreaks after the introduction of *Wolbachia*.
- Generalizing wMel effectiveness estimates across settings will require attention to how immunity, introgression, and transmission risk differ between them.

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