Impact of venereal transmission on the dynamics of vertically transmitted viral diseases among mosquitoes

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MOSQUITO-BORNE DISEASES

- According to WHO, more than half of the world population live in areas where mosquitoes are present.
- Zika, dengue, chikungunya, West Nile, Malaria and yellow fever are all transmitted to humans by mosquitoes.
- In 2015 malaria alone caused 438 000 deaths.
- The worldwide incidence of dengue has risen 30-fold in the past 30 years, and more countries are reporting their first outbreaks of the disease.
- Viruses are transmitted to humans via the female mosquitoes.

VERTICAL TRANSMISSION AND VENEREAL TRANSMISSION

Diseases transmission in mosquito

Vertical transmission (VT)

A vertically transmitted diseases is a diseases caused by pathogens (such as bacteria and viruses) that uses mother-to-child transmission, that is, transmission directly from the mother to an embryo, or baby during pregnancy or childbirth.

Venereal transmission(VNT)

Venereal transmitted diseases are infections that pass from one population to another through sexual contact.

MOTIVATION (VT)

Vertical transmission of viruses within mosquitoes were reported for most of these mosquito-borne diseases in some experimental studies.

- **Japanese encephalitis** *(Science, 1978)*
- **Dengue virus** *(The American journal of tropical medicine and hygiene, 1983)*
- **West Nile virus** *(The American journal of tropical medicine and hygiene, 1993)*
- **Zika virus** *(The American journal of tropical medicine and hygiene, 2016)*
- **Chikungunya** *(Emerging infectious diseases, 2011)*
- **Malaria** *(PLoS pathogens,2008)*
- **Yellow fever virus** *(Transactions of the Royal Society of Tropical Medicine and Hygiene. 1997)*

MOTIVATION (VNT)

- Experimental study on Aedes aegypti mosquitoes for VNT of chikungunya virus by Mavale et. al. They found that infected male mosquitoes are capable of infecting females during mating at a low rate.
  The American journal of tropical medicine and hygiene, 2010

- VNT of zika virus between female and male mosquitoes was confirmed in a recent experiment.
  Memórias do Instituto Oswaldo Cruz, 2018

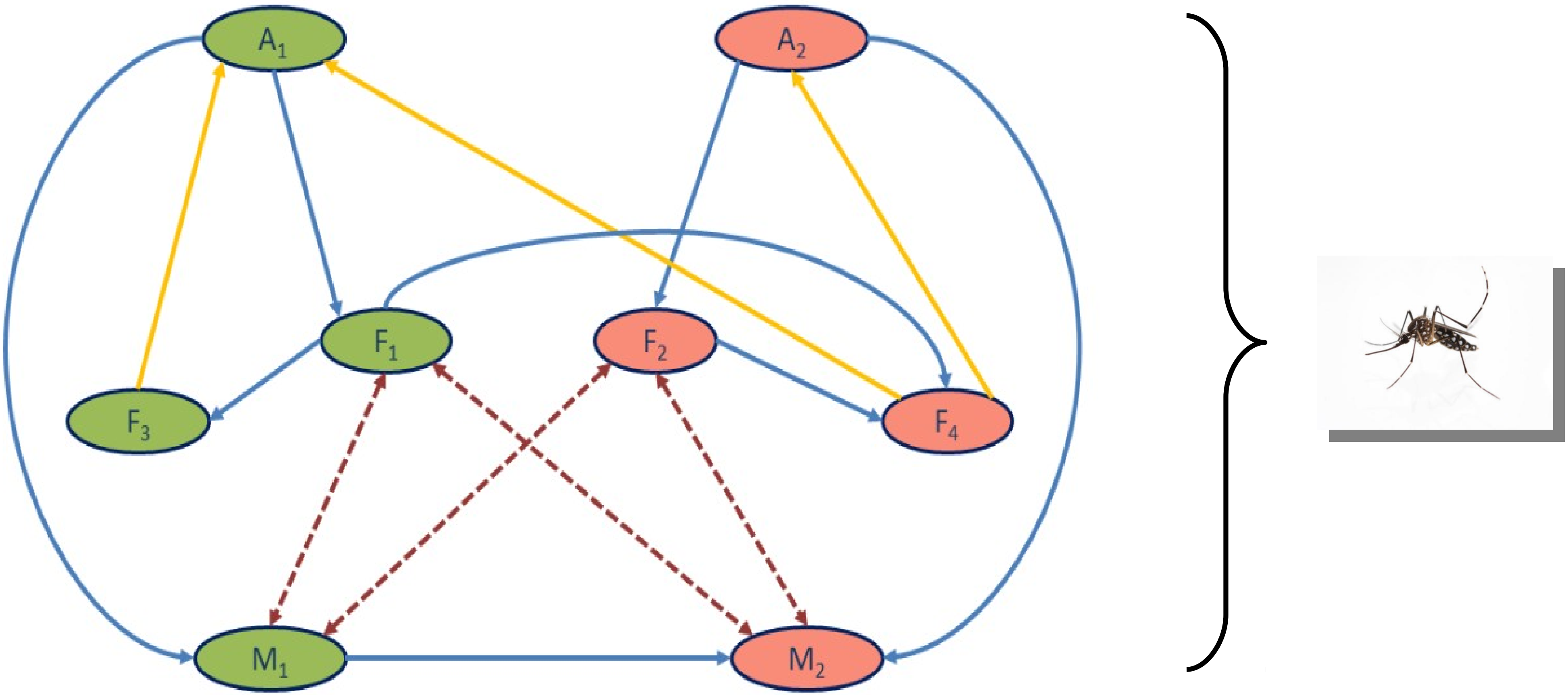
- VNT of DENV in Aedes aegypti have been tested by Sanchez-Vargas et. al. They found that male mosquitoes infected by DENV through VT route were fit for transmitting the infection to uninfected virgin females through mating.
  PLoS neglected tropical diseases, 2018

AIM OF THIS STUDY

- To control mosquito-borne diseases, it is necessary to understand the transmission dynamics between mosquitoes.
- There is a scope of investigating the contribution of VT and VNT on the persistence of the virus theoretically because there is no theoretical study considering both transmission.
- It is important to investigate which transmission route (VT and VNT) is more responsible for the persistence of the virus when there is no host.

We propose and analyze a compartmental model considering mosquito population only.

SCHEMATIC DIAGRAM



The dotted double arrows denote the sexual contacts and single sided arrows represent transition from one compartment to another.

Proposed Model

$$\frac{dA_1}{dt} = r(1 - \frac{A_1 + A_2}{K})(F_3 + (1-\phi)F_4) - (\gamma + \mu_1)A_1$$

$$\frac{dA_2}{dt} = r\phi(1 - \frac{A_1 + A_2}{K})F_4 - (\gamma + \mu_1)A_2$$

$$\frac{dF_1}{dt} = (1-p)\gamma A_1 - \frac{\beta F_1(\alpha_1 M_1 + \alpha_2 M_2)}{M_1 + M_2} - \mu_2 F_1$$

$$\frac{dF_2}{dt} = (1-q)\gamma A_2 - \frac{\beta F_2(\alpha_3 M_1 + \alpha_4 M_2)}{M_1 + M_2} - \mu_2 F_2$$

$$\frac{dF_3}{dt} = \frac{\beta F_1(\alpha_1 M_1 + (1-\theta)\alpha_2 M_2)}{M_1 + M_2} - \mu_2 F_3$$

$$\frac{dF_4}{dt} = \frac{\theta\alpha_2\beta F_1 M_2}{M_1 + M_2} + \frac{\alpha_3\beta F_2 M_1}{M_1 + M_2} + \frac{\alpha_4\beta F_2 M_2}{M_1 + M_2} - \mu_2 F_4$$

$$\frac{dM_1}{dt} = p\gamma A_1 - \frac{\xi_1\beta M_1 F_2}{F_1 + F_2} - \mu_2 M_1$$

$$\frac{dM_2}{dt} = q\gamma A_2 + \frac{\xi_1\beta M_1 F_2}{F_1 + F_2} - \mu_2 M_2$$

Model parameters

Par.	Interpretation	Value	Range
r	Laying rate of fertilized female mosquito	13	12-18
K	Carrying capacity of uninfected aquatic mosquito	2×10^5	-
ϕ	Proportion of infected eggs	0.315	0-1
p	Proportion of uninfected male mosquito	0.5	0-1
q	Proportion of infected male mosquito	0.5	0-1
γ	Per capita development rate	1/8.75	1/9.5-1/8.1
μ_1	Natural death rate of mosquito in aquatic phase	0.02	0.01-0.04
μ_2	Natural death rate of adult mosquito	1/14	1/42-1/8
α_1	Successful mating probability	0.4	0-1
α_2	Successful mating probability	0.3	0-1
α_3	Successful mating probability	0.4	0-1
α_4	Successful mating probability	0.3	0-1
ξ_1	Successful mating probability	0.5	0-1
β	Contact rate between male and female mosquito	1	-
θ	proportion of infected fertilized female mosquito	0.5	0-1

BASIC OFFSPRING NUMBER

Disease free equilibrium : $P^0 = (A_1^0, 0, F_1^0, 0, F_3^0, 0, M_1^0, 0)$

where
$$A_1^0 = K\left(1 - \frac{1}{R^*}\right), M_1^0 = \frac{p\gamma}{\mu_2} A_1^0,$$
$$F_1^0 = \frac{(1-p)\gamma}{\alpha_1\beta + \mu_2} A_1^0, F_3^0 = \frac{\alpha_1\beta(1-p)\gamma}{\mu_2(\alpha_1\beta + \mu_2)} A_1^0$$

$$R^* = \frac{r\alpha_1\beta(1-p)\gamma}{\mu_2(\alpha_1\beta + \mu_2)(\gamma + \mu_1)}$$
represents the basic offspring number of mosquito population.

Basic offspring number of mosquito is the average number of uninfected female mosquitoes produced by a single uninfected female mosquito.

To maintain the mosquito population in nature, the necessary condition is $R^* > 1$.

BASIC REPRODUCTION NUMBER

The basic reproduction number at DFE P^0 is given by

$$R_0 = max\{R_1, R_2\}$$

$$R_1 = \frac{(1-p)\gamma\alpha_1\beta r(1-\frac{A_1^0}{K})}{\mu_2(\frac{r}{K}F_3^0+\gamma+\mu_1)(\beta\alpha_1+\mu_2)}$$

$$R_2 = \frac{r\phi(1-\frac{A_1^0}{K})[(1-q)\gamma((\mu_2\alpha_3\beta+\theta\alpha_2\xi_1\beta^2)+q\gamma(\beta\alpha_3+\mu_2)\frac{\theta\alpha_2\beta F_1^0}{M_1^0}]}{\mu_2^2(\beta\alpha_3+\mu_2)(\gamma+\mu_1)}$$

The diseases free equilibrium (DFE) $P^0 = (A_1^0, 0, F_1^0, 0, F_3^0, 0, M_1^0, 0)$ of the system is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Complete-Infection Equilibrium (CIE)

We found the CIE when the vertical transmission is perfect (φ=1), that is when fertilized female mosquito produced all infected offspring.

CIE of the system is which is denoted by P_c is

$$A_1^c = 0, A_2^c = K\left(1 - \frac{1}{R_{CIE}}\right), F_1^c = 0, F_2^c = \frac{(1-q)\gamma}{\alpha_4\beta + \mu_2} A_2^c,$$

$$F_3^c = 0, F_4^c = \frac{\alpha_4\beta(1-q)\gamma}{\mu_2(\alpha_4\beta + \mu_2)} A_2^c, M_1^c = 0, M_2^c = \frac{q\gamma}{\mu_2} A_2^c.$$

$R_{CIE} = \dfrac{\phi r \alpha_4 \beta(1-q)\gamma}{\mu_2(\gamma + \mu_1)(\alpha_4\beta + \mu_2)}$ is the next generation number for the infected population representing the number of infected eggs that one infected egg generate in one life cycle of a mosquito.

The complete-infection equilibrium Pc of the system is locally asymptotically stable if

$$R_{CIE} > max\{1, (1-\theta)\frac{\alpha_1\beta + \mu_2}{\alpha_2\beta + \mu_2} R^*\}.$$

Endemic Equilibrium

Endemic equilibrium of this system is denoted by $P^* = (A_1^*, A_2^*, F_1^*, F_2^*, F_3^*, F_4^*, M_1^*, M_2^*)$ and given by

$$A_1^* = \frac{K}{1+r_{21}}\left(1 - \frac{1}{G^*}\right), A_2^* = r_{21}A_1^*, F_1^* = \frac{(1-p)\gamma A_1^*}{\beta\alpha_1 m_1^* + \beta\alpha_2 m_2^* + \mu_2},$$

$$F_2^* = \frac{(1-q)\gamma r_{21}A_1^*}{\beta\alpha_3 m_1^* + \beta\alpha_4 m_2^* + \mu_2}, F_3^* = \frac{\beta F_4^*(\alpha_1 m_1^* + (1-\theta)\alpha_2 m_2^*)}{\mu_2},$$

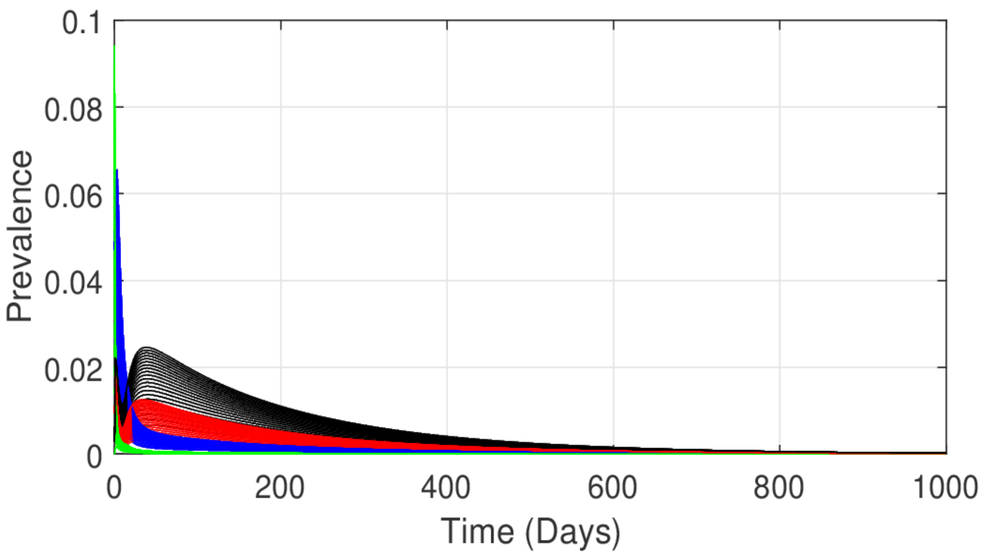
$$F_4^* = \frac{\theta\alpha_2\beta F_1^* m_1^* + \alpha_3\beta F_2^* m_1^* + \alpha_4\beta F_2^* m_2^*}{\mu_2},$$

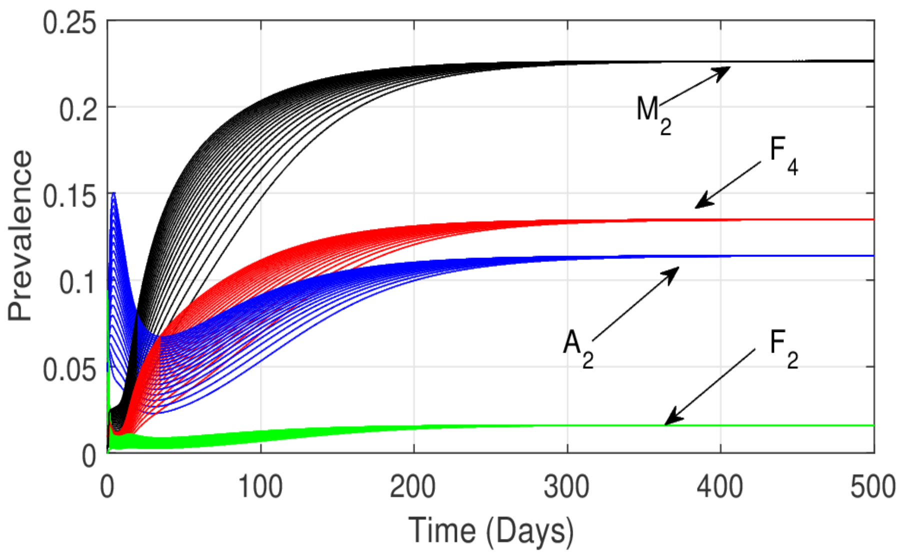
$$M_1^* = \frac{p\gamma A_1^*}{\xi_1\beta f_2^* + \mu_2}, M_2^* = \frac{q\gamma r_{21}A_1^* + \xi_1\beta M_1^* f_2^*}{\mu_2}$$

Where

$$G^* = \frac{r\phi F_4^*}{(\gamma+\mu_1)r_{21}A_1^*}, f_2^* = \frac{F_2^*}{F_1^*+F_2^*}, m_1^* = \frac{M_1^*}{M_1^*+M_2^*}, m_2^* = \frac{M_2^*}{M_1^*+M_2^*}$$

GLOBAL STABILITY



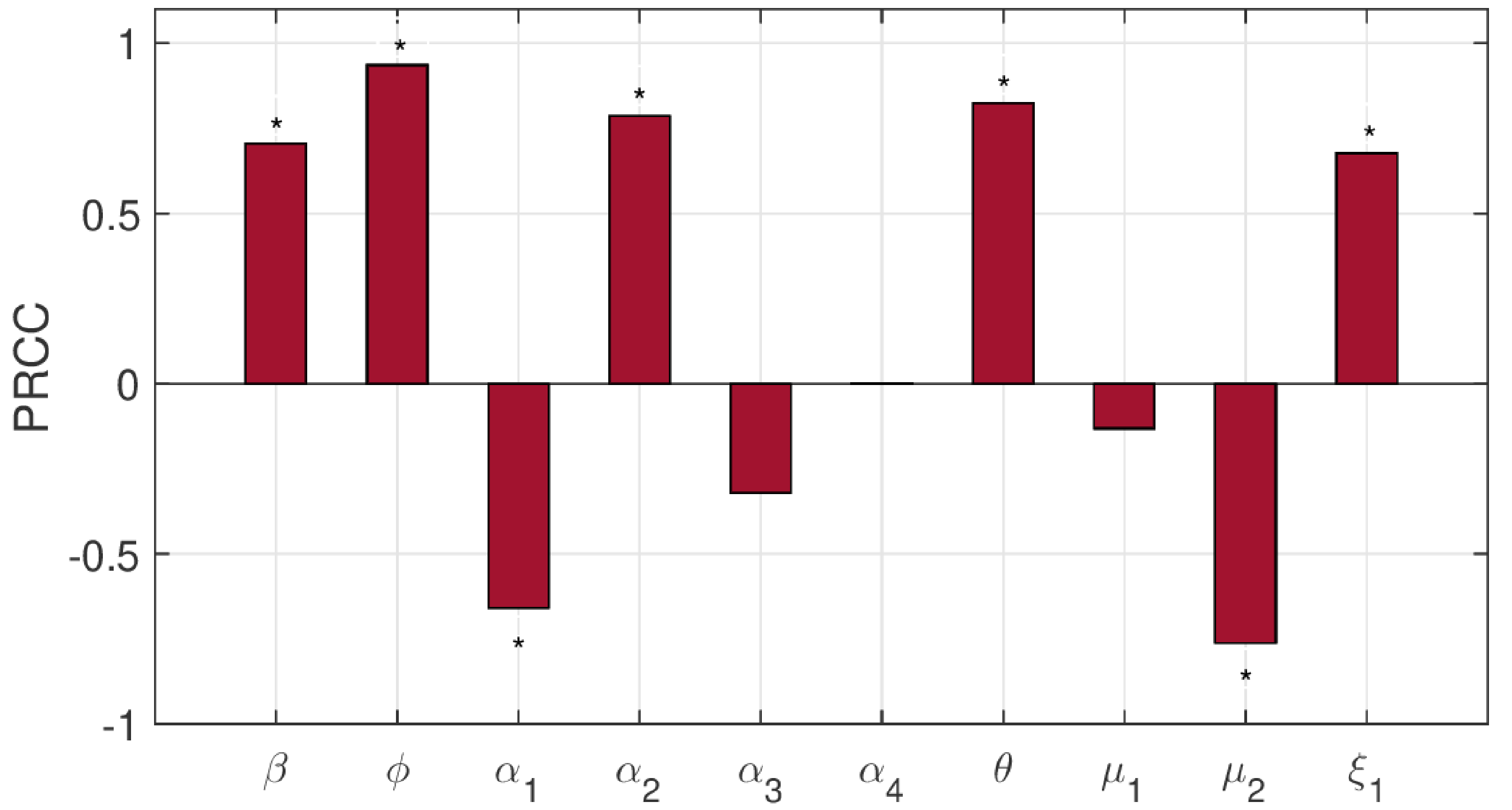


$\varphi = 0.245$
(corresponding $R_0 = 0.8516 < 1$)

$\varphi = 0.555$
(corresponding $R_0 = 1.9291 > 1$)

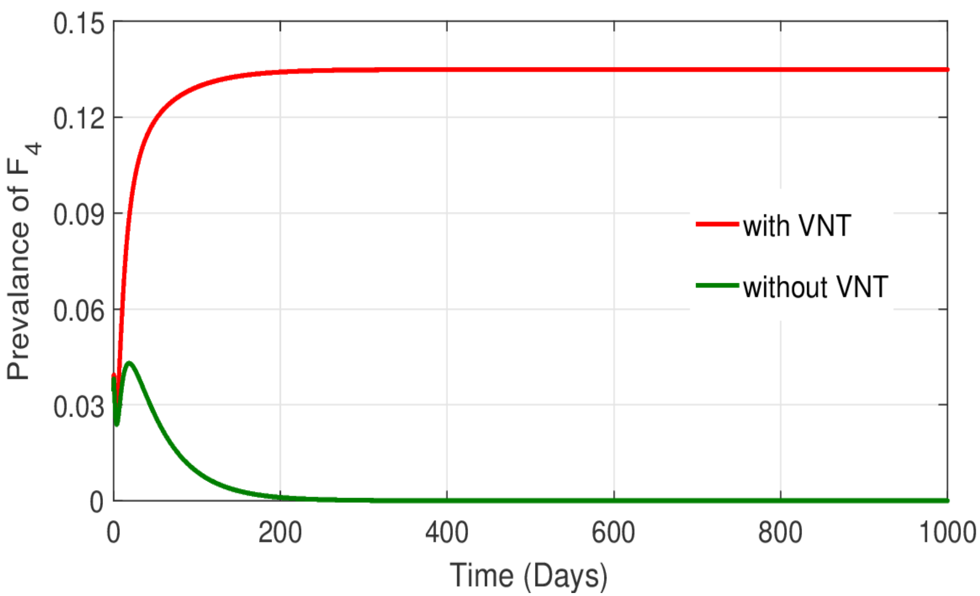
It is observed that the solutions converge to the endemic equilibrium irrespective of different initial conditions and values of R_0 .

SENSITIVITY ANALYSIS

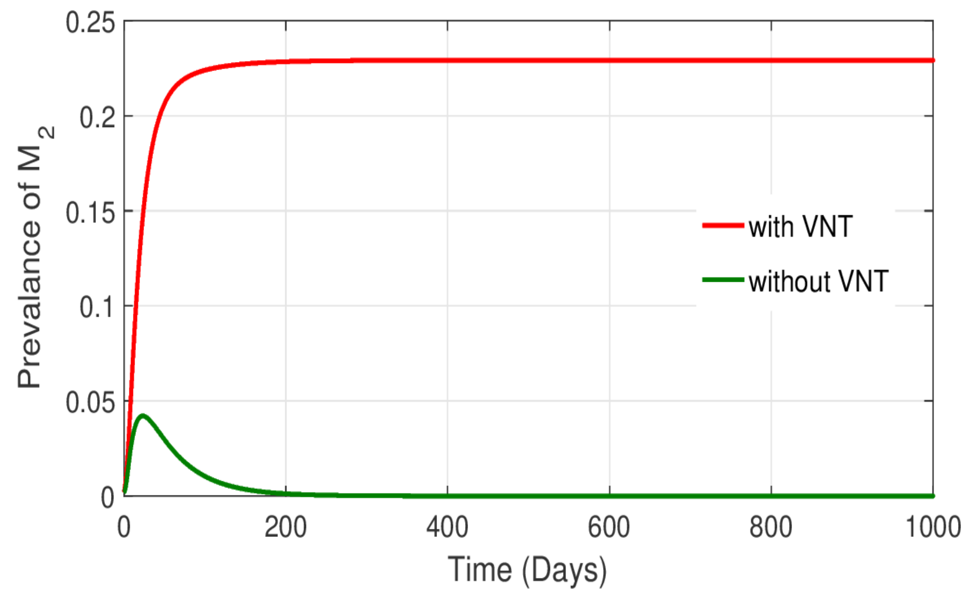


Effect of uncertainty of the model on total infected pregnant female mosquitoes (F_4^{total}).

EFFECT OF SEXUAL TRANSMISSION



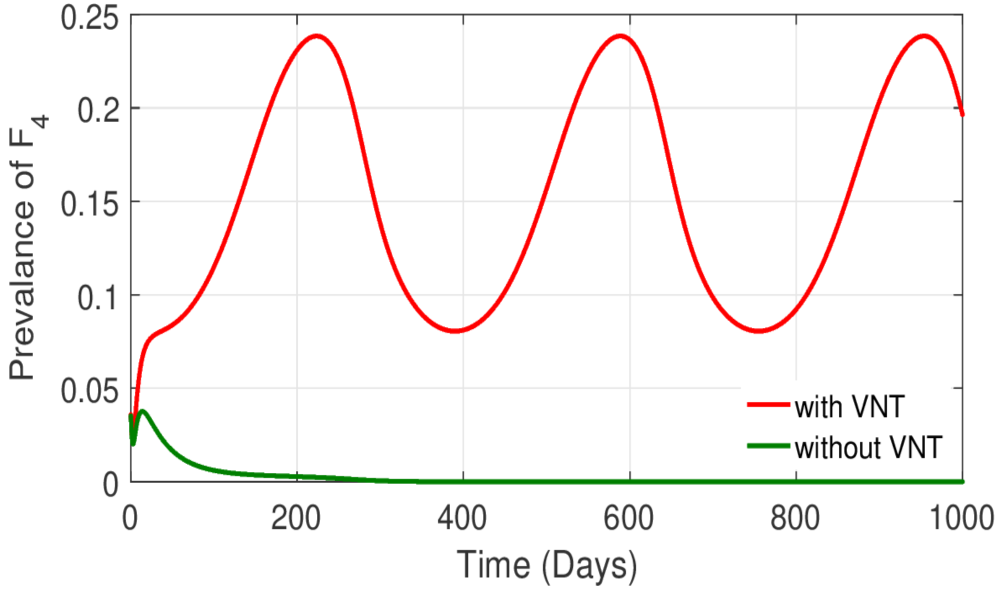
Infected fertilized females (F_4)



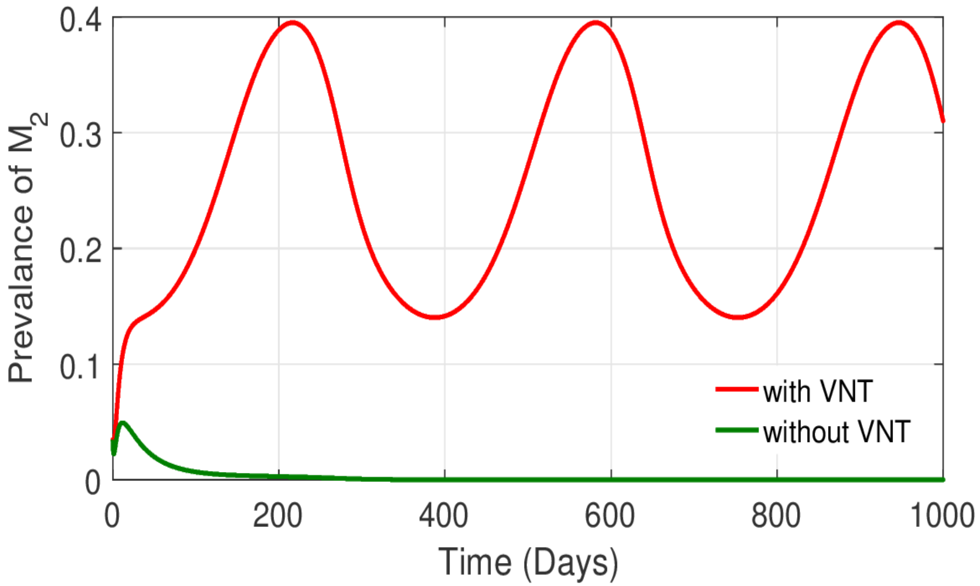
Infected males (M_2)

The infected populations M_2 and F_4 remains persistent at a small value whenever sexual transmission occurs. On the other hand, the infection prevalence converges to zero for the system without venereal transmission

EFFECT OF SEXUAL TRANSMISSION



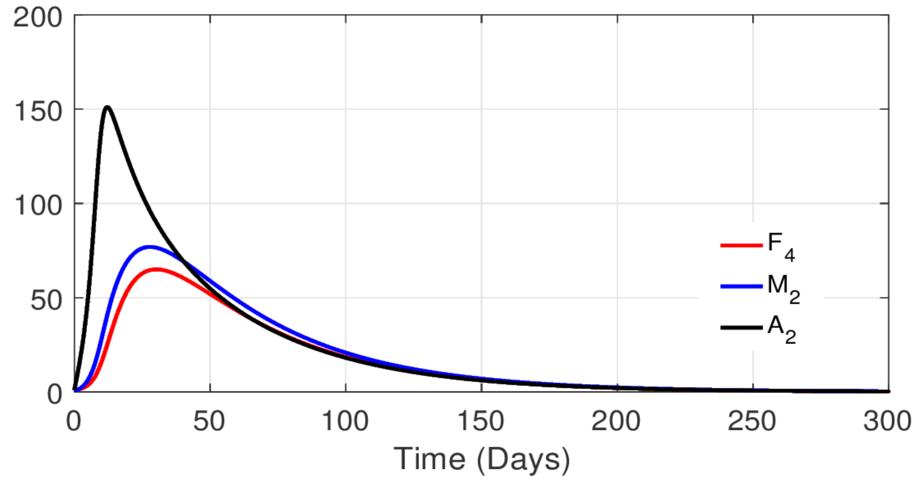
Infected fertilized females (F_4)



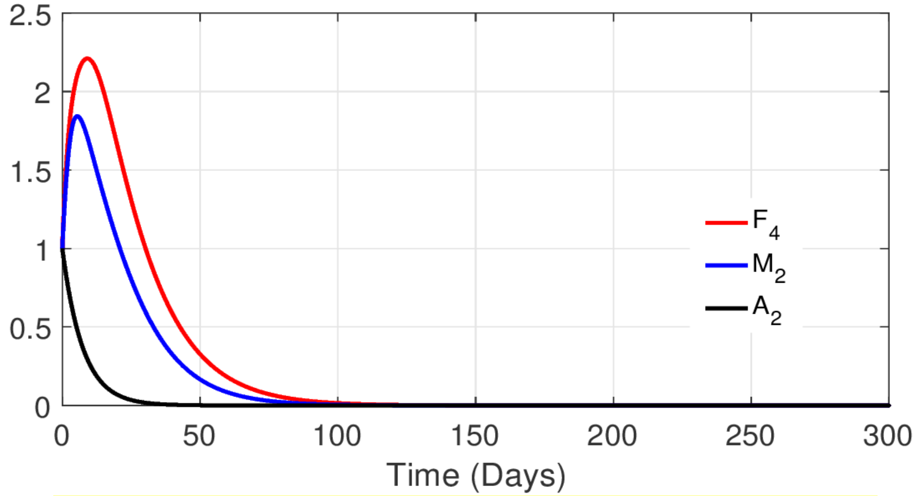
Infected males (M_2)

Further, to investigate the robustness of this phenomenon, we simulate the model with seasonal forcing. Infected mosquitoes persist for venereal transmission and die out when there is no venereal transmission.

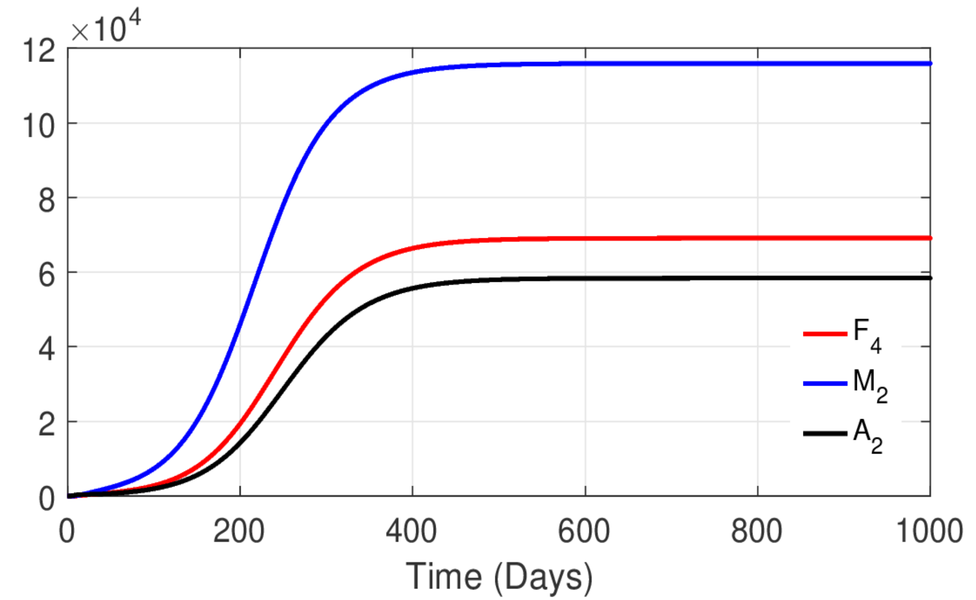
Comparison of Two Transmission Routes



Without VNT (ξ_1 = 0, θ = 0, φ = 0.555)



Without VT (ξ_1 = 0.4, θ = 0.5, φ = 0)



With both transmission (ξ_1 = 0.4, θ = 0.5, φ = 0.555)

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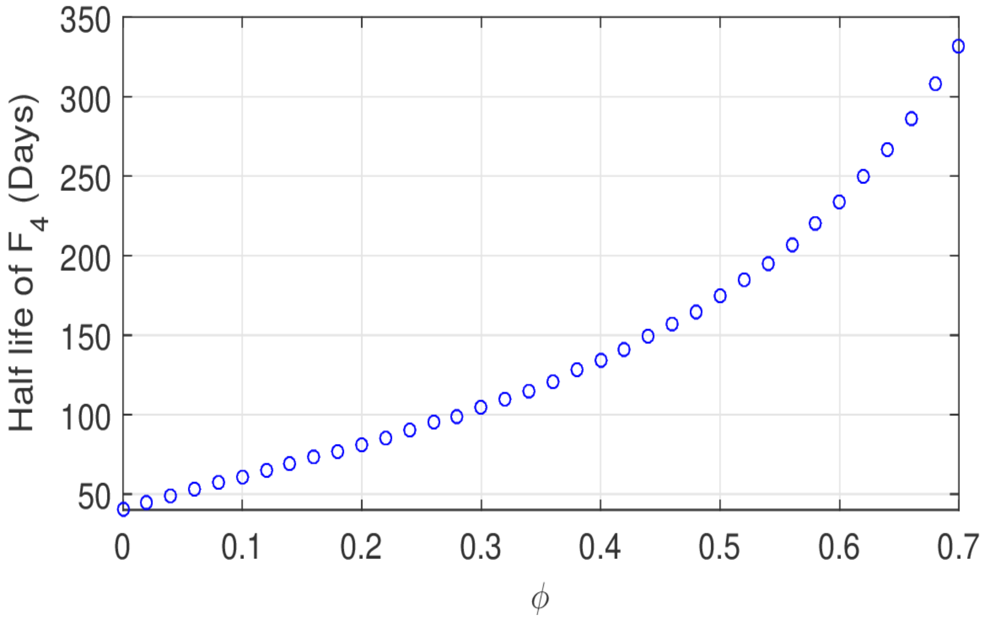
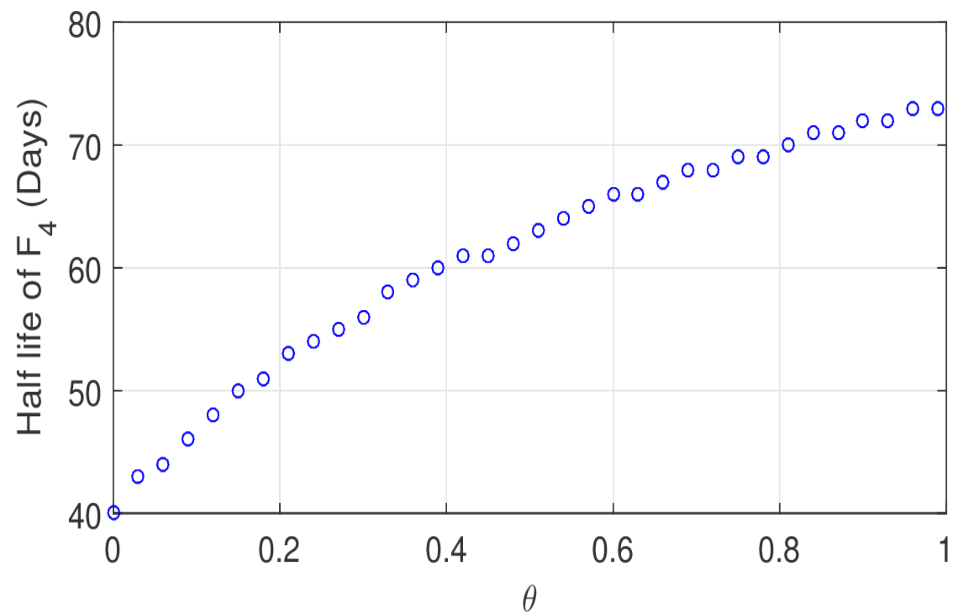
HALF LIFE

The half life of a population is defined by the time taken to reduce the initial population by 50%.



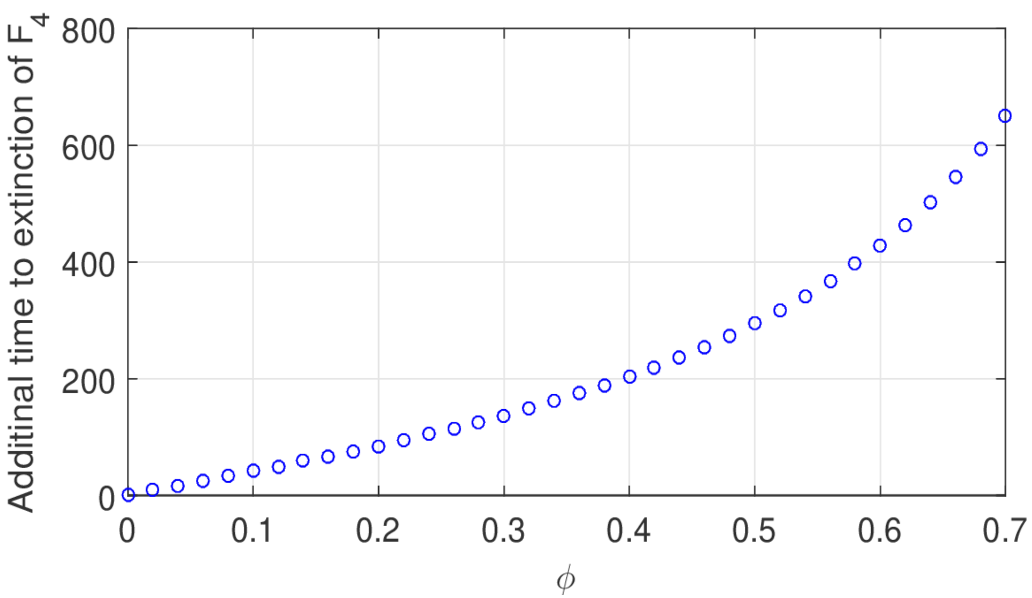
Time taken to reach the half life of F_4 population when there is only vertical transmission



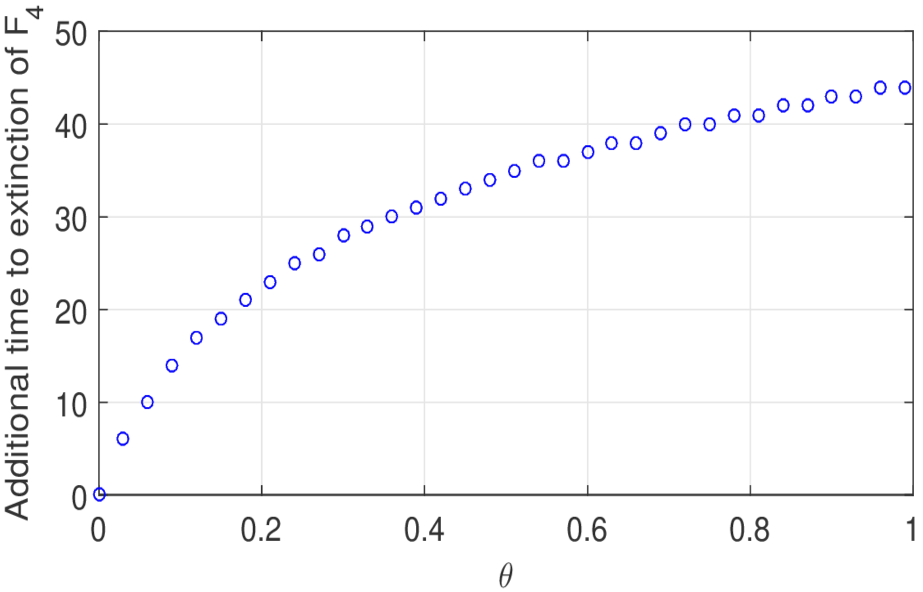
Time taken to reach the half life of F_4 population when there is only venereal transmission through male-to-female route

ADDITIONAL TIME TO EXTINCTION

Additional time to extinction in presence of VT (or VNT) is calculated by the difference between time taken to extinction when there is neither VT nor VNT and time taken to extinction when there is VT (or VNT) only.

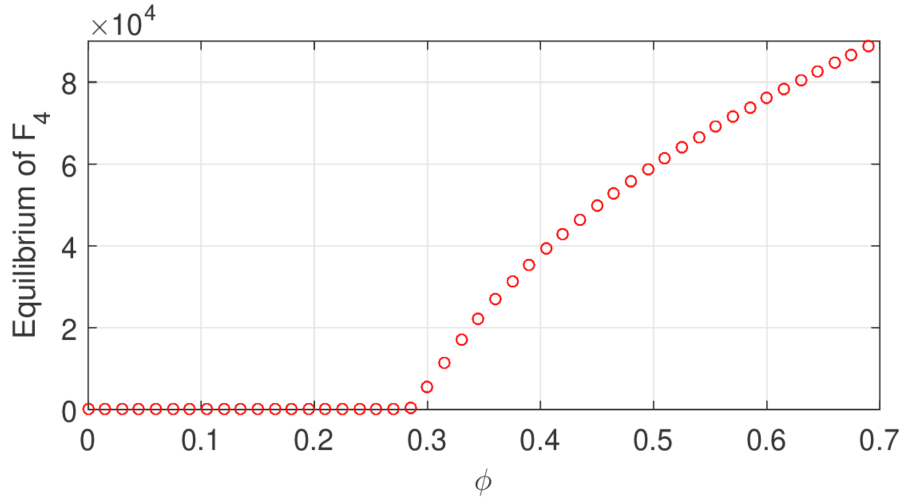


Additional time taken for the infected fertilized females to fall to 1 for only VT

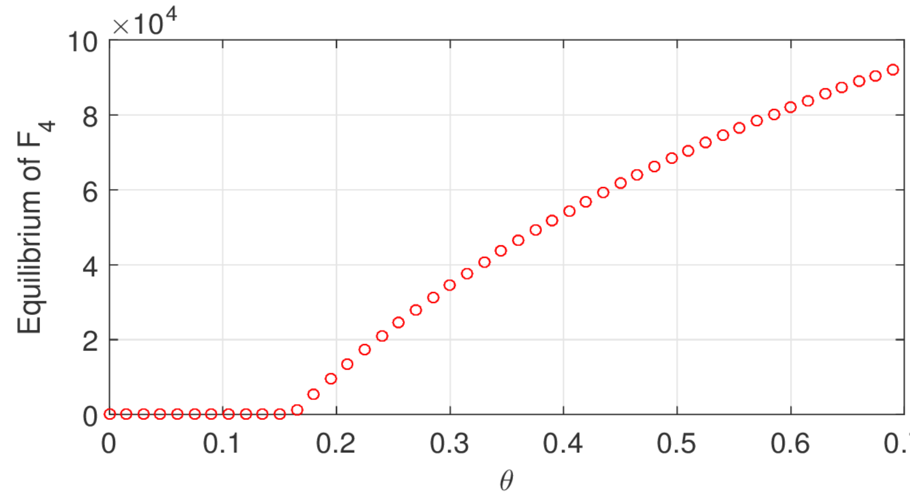


Additional time taken for the infected fertilized females to fall to 1 for only VNT

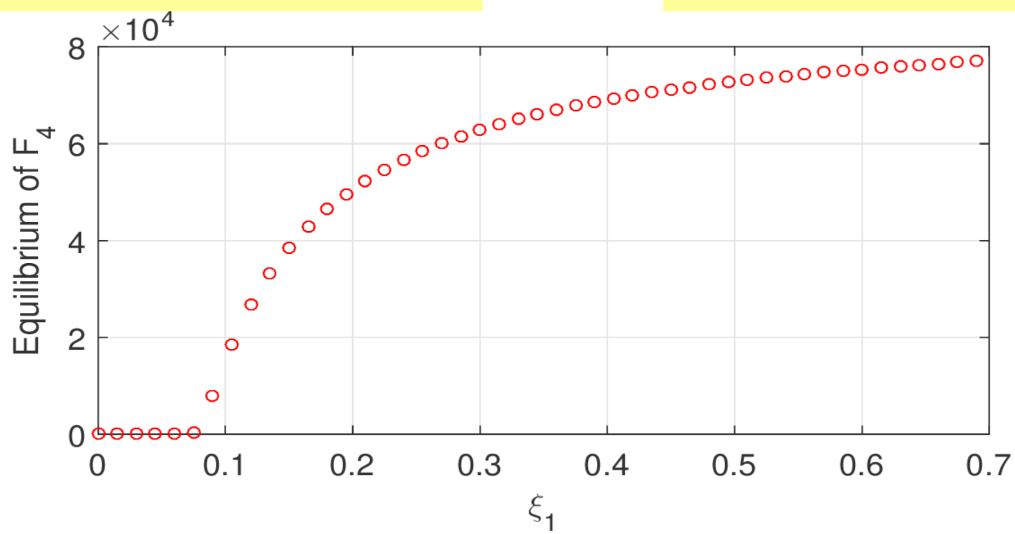
THRESHOLD BEHAVIOR OF TRANSMISSION PARAMETERS



$0 < \varphi < 0.7$ ($\theta = 0.5$ and $\xi_1 = 0.4$)



$0 < \theta < 0.7$ ($\varphi = 0.555$ and $\xi_1 = 0.4$)



$0 < \xi_1 < 0.7$ ($\varphi = 0.555$ and $\theta = 0.5$)

Threshold value:
φ=0.285,
θ=0.15
ξ_1 = 0.075

CONCLUSION

- The infected populations M_2 and F_4 remains persistent at a small value whenever sexual transmission occurs and the infection prevalence converges to zero for the system without VNT.
- The virus persists whenever there is venereal transmission remains in both seasonal and non-seasonal settings.
- If both the transmission routes are active then all the three infected compartments approach a non-zero equilibrium size.
- VT is more effective in maintaining high endemic levels of infected fertilized female mosquito as compared to VNT with respect to half life.
- The parameters φ (related to VT), θ and ξ_1 (related to VNT) show threshold like behavior for the equilibrium values of infected mosquito population.

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Thank you