Research article

The impact of mating competitiveness and incomplete cytoplasmic incompatibility on *Wolbachia*-driven mosquito population suppression

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Abstract: To control mosquito-borne diseases such as dengue, malaria, and Zika, *Wolbachia*-infected male mosquitoes have been released in open areas to suppress wild mosquito population driven by cytoplasmic incompatibility (CI). In this work, we initiate a preliminary assessment on how the CI intensity ξ, and the mating competitiveness μ of released males relative to wild males, impact the suppression efficacy by a delay differential equation model. Our analysis identifies a threshold CI intensity $\xi_0 \in (0, 1)$ as an increasing function of the natural reproduction rate of the wild mosquitoes, and a threshold value r^* for the ratio $r(t)$ between the numbers of released males and wild males. The population suppression fails when $\xi \leq \xi_0$, and succeeds when $\xi > \xi_0$ and $r(t) \geq r^*$. Our analyses indicate that ξ plays a more important role than μ in the population suppression. For instance, a slight decrease of ξ from 1 to 0.92 is more devastating than halving μ from 1 to 0.5. In our estimation of the optimal starting date for infected male release to target a more than 95% wild population reduction during the peak season of dengue in Guangzhou, we find that the optimal date is almost independent of μ but is sensitive to ξ. If CI is complete, then starting about two months ahead can be an optimal option for less financial and labor costs. A slight reduction in the CI intensity requires a considerably earlier starting date.

Keywords: mosquito-born diseases; *Wolbachia*; cytoplasmic incompatibility; mosquito population suppression; delay differential equation

In Memory of Geoffrey J. Butler and Herbert I. Freedman

1. Introduction

The invasive Asian tiger mosquito *Aedes albopictus*, originally indigenous to Southeast Asia, has invaded most continents, including Africa, Europe, and the Americas, prompted by international travel and trade, especially the used tire trade [1, 2]. As a competent vector of more than 25 viruses such as dengue, Zika, and chikungunya, *Aedes albopictus* is a species of great medical concern in the world. It is the sole transmission vector of dengue in southern China. In 2014, an unprecedented outbreak of dengue fever hit Guangzhou, the capital city of Guangdong province, with 37,354 laboratory confirmed cases of infection [3].

With no effective therapies or licensed vaccines available, the dominating dengue control strategy has been vector elimination, including community-based source reduction and insecticide spraying. However, the invasiveness of *Aedes albopictus* and the creation of ubiquitous larval sources make source reduction a challenging task, while heavy insecticide applications induce serious environmental pollution and the insecticide resistance [1, 2, 4]. Fortunately, novel disease control methods using the endosymbiotic bacterium *Wolbachia* have been developed since the pioneering study of Xi et al. [5] in 2005. The success of the methods can be attributed mostly to the following facts: *Biological safety* : *Wolbachia* are naturally presented in up to 60% of insects, but are not usually found in the *Aedes aegypti* mosquito that transmits human viruses [6]. *Virus control* : The infection of some *Wolbachia* strains such as wMel has shown to block the transmission of dengue and other viruses in both *Aedes aegypti* and *Aedes albopictus* [6, 7, 8, 9]. *Maternal transmission* : The bacterium is transmitted from infected females to the next generation. *Cytoplasmic incompatibility* (CI): If a *Wolbachia* strain is infected by a male mosquito, but not by a female, then their crossing is incompatible that induces zygotic death and female sterility [5, 6, 8, 9].

These tantalizing properties have engineered two *Wolbachia*-driven approaches for the elimination of mosquito borne diseases: population replacement and population suppression of wild *Aedes* mosquitoes. In the first approach, both male and female mosquitoes infected by a *Wolbachia* strain are released in natural areas. If the released numbers exceed a threshold level, then the reproduction advantage of the infected females driven by the CI mechanism and maternal transmission can facilitate the spread and fixation of *Wolbachia* in the wild mosquito population [10]. In the second approach, only infected males are released in natural areas. The incompatible crossing between the released males and the wild females induces female sterility and a suppression of the next generation [8, 11]. These developments have stimulated extensive research activities in mathematical ecology to study the *Wolbachia* interfered population dynamics of mosquitoes [10, 11, 12, 13, 14]. In recent years, we have estimated the threshold release level for *Wolbachia* fixation and quantified how this critical level is affected by various factors such as the spatial movement of mosquitoes [15, 16], the randomness of climatic conditions [17, 18, 19], and the leakage of maternal transmission [20, 21, 22]. More recently, we have also assessed the sensitivity of system parameters on the efficacy of *Wolbachia* driven *Aedes* mosquito suppression [23, 24, 25].

Let $\mu \geq 0$ denote the *mating competitiveness* of the male mosquitoes infected by a *Wolbachia* strain comparing to wild males in the competition for wild female mating. Let $\xi \in [0, 1]$ denote the *CI intensity* – the zygotic death rate from the incompatible crossing of infected males and wild females. In the modeling of *Wolbachia* interfered mosquito dynamics so far, it has been almost always assumed that released males are equally competitive as wild males with $\mu = 1$, and the CI is complete with

$\xi = 1$. These assumptions are indeed strongly supported by the experiments in laboratory or even in the semi-field cages [8, 11]. However, the field trials of *Aedes albopictus* population suppression in Guangzhou since 2015 have revealed a significant reduction in the competitiveness with μ ranging from 0.50 to 0.75 in wild areas [8, 11, 26]. In fact, wild *Aedes albopictus* mosquitoes in Guangzhou are naturally infected with two *Wolbachia* strains wAlbA and wAlbB. It is the infection of the third type of *Wolbachia* strain, wPip, established by embryonic micro-injections, that blocks virus transmission and induces CI in the crossing of triple-infected males and double-infected females [8]. Although the CI intensity is found to be strong with $\xi \geq 0.95$, it does indicate a possibility that CI may not be complete.

In this work, we initiate a preliminary assessment on how the reduced mating competitiveness and incomplete CI impair the efficacy of the *Wolbachia*-driven population suppression of *Aedes* mosquitoes in natural areas. This is of primary importance for designing more effective mosquito release policies in the planned large scale mosquito suppression campaign. We consider a population of wild adult mosquitoes in a total number $A(t)$ at time t in the studying area, evenly divided in sex, that are interfered by $R(t)$ released male adults infected by a *Wolbachia* strain not presented in the natural population. If the released males are equally competitive as wild males in mating, then the chance for a female to mate a released male, or the incompatible crossing probability, equals $R(t)$ over the total number $A(t)/2+R(t)$ of all males. In general, as the contribution of released males is scaled by the mating competitiveness μ, the incompatible crossing probability becomes $\mu R(t)/[A(t)/2 + \mu R(t)]$. The offsprings produced by a female consist of two parts: those from compatible crossings, and those from incompatible crossings reduced by CI. Assume that the waiting time from the mating to the eclosion of next generation takes τ days, and each female produces b adult offsprings per day on average in compatible crossings. The delay τ changes with the climate and nutrient conditions and varies from 16 days to 66 days for *Aedes albopictus* in Guangzhou [27, 28, 29]. By taking account of the compatible and incompatible crossings and the CI intensity into consideration, we obtain the expected number of adults on day t produced by a single female on day $t - \tau$ as

$$b \cdot \frac{A(t - \tau)/2}{A(t - \tau)/2 + \mu R(t - \tau)} + b(1 - \xi) \cdot \frac{\mu R(t - \tau)}{A(t - \tau)/2 + \mu R(t - \tau)}. \tag{1.1}$$

By multiplying theses terms with the total number of females, $A(t-\tau)/2$, on day $t-\tau$, we obtain the eclosion rate on day t. For the mortality terms, we follow the idea of Herb Freedman in the description of the classical logistic model [30]: For small $A(t)$ the population decays linearly with a minimum mortality rate $m > 0$; for large $A(t)$ the mosquitoes "compete each other for the limited resources" in the breeding sites in the larval stage and the decay is dominated by a second order term. In summary, we set

$$\frac{dA(t)}{dt} = \frac{b}{2} \frac{A(t - \tau) + 2(1 - \xi)\mu R(t - \tau)}{A(t - \tau) + 2\mu R(t - \tau)} A(t - \tau) - m\left(1 + \frac{A(t)}{K}\right)A(t). \tag{1.2}$$

The constant K plays the role that characterizes the density restriction as in the logistic model, but is not the carrying capacity due to the complexity of the eclosion terms and the factor m. If we set $r(t) = 2R(t)/A(t)$, the ratio of the released male numbers over the wild male numbers, then (1.2) is converted to

$$\frac{dA(t)}{dt} = \frac{b}{2} \frac{1 + \mu(1 - \xi)r(t - \tau)}{1 + \mu\, r(t - \tau)} A(t - \tau) - m\left(1 + \frac{A(t)}{K}\right)A(t). \tag{1.3}$$

In accordance with their biological meanings, we maintain the following conditions for the system parameters:

$$b, \tau, K > 0; \quad m \in (0, 1); \quad \mu \geq 0; \quad \xi \in [0, 1]. \tag{1.4}$$

The solution of (1.3) subject to the initial condition $A(t) = \phi(t) \in C([t_0 - \tau, t_0], (0, \infty))$ for $t \in [t_0 - \tau, t_0]$, $t_0 \geq 0$, will be denoted by $A(t) = A(t, t_0, \phi)$.

We assess the impact of the mating competitiveness μ and the CI intensity ξ on the suppression efficacy of wild *Aedes* mosquitoes, by analyzing the global dynamics of (1.3) and performing numerical simulations with the experimental data. Our analysis identifies a threshold CI intensity $\xi_0 \in (0, 1)$ that increases in the reproduction of wild mosquitoes. When $\xi \leq \xi_0$, the population suppression is improbable no matter how many infected males are released. For $\xi > \xi_0$, we find a threshold release ratio $r^* > 0$: If $r(t)$ is kept at a low level with $\bar{r} = \sup_{[0,\infty)} r(t) < r^*$, then $A(t)$ is bounded below by a positive constant depending on $\bar{r}$; if $r(t) \geq r^*$ for large t, then $\lim_{t \to \infty} A(t) = 0$. Our theorems are inclined to support a more important role of ξ than μ in the population suppression. It is further supported by our numerical examples which show that a slight decrease of ξ from 1 to 0.92 is more devastating than halving μ from 1 to 0.5. The CI intensity ξ_0 not only warns an absolute failure of the population suppression when $\xi < \xi_0$, it also predicts a great challenge of mosquito control when ξ is not considerably higher than ξ_0. Finally, we estimate the optimal starting date for infected male release to target a more than 95% reduction of the wild population on October 1, normally in the middle of the peak season for mosquito growth and dengue fever transmission in Guangzhou. We find that the optimal date is almost independent of μ but is sensitive to ξ. If CI is complete, then starting about two months ahead can be an optimal option for less financial and labor costs. A slight reduction in the CI intensity may require not only more male releases, but also a considerably earlier starting date.

2. The threshold levels for population suppression

We estimate the thresholds for population suppression of wild *Aedes* mosquitoes by studying the global dynamics of (1.3). We begin with the following simple and fundamental result.

Lemma 2.1. *For each $\phi \in C([t_0 - \tau, t_0], (0, \infty))$, the solution $A(t) = A(t, t_0, \phi)$ of (1.3) is positive and bounded in $t > t_0$.*

Proof. Suppose for contradiction that $A(t) > 0$ does not hold for all $t > t_0$. Then we may find a $t_1 > t_0$ such that $A(t) > 0$ in $[t_0 - \tau, t_1)$ and $A(t_1) = 0$. As A vanishes the first time at t_1, we have $A'(t_1) \leq 0$, which contradicts

$$A'(t_1) = \frac{b}{2} \frac{1 + \mu(1 - \xi)r(t_1 - \tau)}{1 + \mu r(t_1 - \tau)} A(t_1 - \tau) > 0$$

obtained from (1.3). If $A(t)$ is unbounded, then there exists a sequence $\{t_n\}$, with $t_n \to \infty$ as $n \to \infty$, such that $A'(t_n) \geq 0$, $A(t_n - \tau) \leq A(t_n)$, $A(t_n) \to \infty$ as $n \to \infty$. Substituting $t = t_n$ into (1.3) and applying these conditions yield

$$m\left(1 + \frac{A(t_n)}{K}\right) \leq \frac{b}{2} \frac{1 + \mu(1 - \xi)r(t_n - \tau)}{1 + \mu r(t_n - \tau)} \leq \sup_{x \geq 0} \frac{b}{2} \frac{1 + \mu(1 - \xi)x}{1 + \mu x},$$

which is apparently incompatible with the unboundedness of A. $\qquad\square$

2.1. The lower bound of the CI intensity

As b counts the average number of adult offspring produced by a single female per day in compatible crossings, while $m \in (0, 1)$ is the average daily mortality rate of adults, it holds in normal environmental conditions that $b > 2m$, that is,

$$\xi_0 = 1 - \frac{2m}{b} > 0. \tag{2.1}$$

As in [25], we will also maintain this condition in the following studies. Interestingly, our next result shows that ξ_0 defines a lower bound on the CI intensity below which population suppression is, independent of releasing efforts, absolutely improbable.

Theorem 2.1. *If the CI intensity $\xi < \xi_0$, then it holds uniformly that*

$$\underline{A} = \liminf_{t \to \infty} A(t) \geq \frac{bK(\xi_0 - \xi)}{2m} > 0, \tag{2.2}$$

independent of the initial function $\phi \in C([t_0 - \tau, t_0], (0, \infty))$ and the releasing amount $R(t)$.

Proof. We first prove $\underline{A} > 0$. Suppose for contradiction that it is not true. Then $\underline{A} = 0$. For an arbitrary initial function $\phi \in C([t_0 - \tau, t_0], (0, \infty))$, let ϕ_0 denote its absolute minimum value on $[t_0 - \tau, t_0]$. For each $n = 1, 2, \cdots$, define t_n as the least time at which A reaches $\phi_0/(n + 1)$. By the assumption $\underline{A} = 0$, t_n is well-defined, and

$$A(t) > A(t_n) = \frac{\phi_0}{n + 1} \quad \text{for} \quad t \in [t_0 - \tau, t_n), \quad A'(t_n) \leq 0, \quad \lim_{n \to \infty} t_n = \infty. \tag{2.3}$$

Let $t = t_n$ in (1.3). We then have

$$m\left(1 + \frac{A(t_n)}{K}\right)A(t_n) \geq \frac{b}{2}\frac{1 + \mu(1 - \xi)r(t_n - \tau)}{1 + \mu\, r(t_n - \tau)}A(t_n - \tau).$$

As $A(t_n - \tau) > A(t_n)$, the inequality remains valid after replacing $A(t_n - \tau)$ by $A(t_n)$. Reorganizing terms slightly leads to

$$1 + \frac{A(t_n)}{K} \geq \frac{b}{2m}\frac{1 + \mu(1 - \xi)r(t_n - \tau)}{1 + \mu\, r(t_n - \tau)}.$$

Because $[1 + \mu(1 - \xi)x]/(1 + \mu x)$ decreases in $x \geq 0$, by using (2.1) we find further that

$$1 + \frac{A(t_n)}{K} > \frac{b(1 - \xi)}{2m} \quad \Rightarrow \quad A(t_n) > K\left[\frac{b(1 - \xi)}{2m} - 1\right] = \frac{bK(\xi_0 - \xi)}{2m}.$$

This is obviously inconsistent with (2.3) when n is sufficiently large and verifies $\underline{A} > 0$.

By using the *fluctuation lemma*, see Lemma A.1 in [31], we can find a sequence $\{s_n\}$ such that $s_n \to \infty$, $A(s_n) \to \underline{A}$ and $A'(s_n) \to 0$ as $n \to \infty$. Let $t = s_n$ in (1.3). We obtain

$$m\left(1 + \frac{A(s_n)}{K}\right)A(s_n) \geq \frac{b(1 - \xi)}{2}A(s_n - \tau) - A'(s_n)$$

whose infimum limit with $n \to \infty$ yields

$$m\left(1 + \frac{\underline{A}}{K}\right)\underline{A} \geq \frac{b(1 - \xi)}{2}\underline{A}.$$

from which (2.2) follows at once. $\qquad \square$

In the special case of $\xi = \xi_0$, no meaningful conclusion can be made from Theorem 2.1 since the low bound in (2.2) equals zero. The following theorem shows that $A(t)$ is still bounded below by a positive constant which depends on the upper bound of the releasing ratio $r(t)$.

Theorem 2.2. *Assume that the CI intensity $\xi = \xi_0$ and $\bar{r} = \sup_{[t_0-\tau,\infty)} r(t) < \infty$. Then*

$$\underline{A} = \liminf_{t\to\infty} A(t) \geq \frac{bK\xi_0}{2m(1+\mu\bar{r})} > 0 \tag{2.4}$$

for any initial function $\phi \in C([t_0 - \tau, t_0], (0, \infty))$.

Proof. Similar to the proof of Theorem 2.1, we first prove $\underline{A} > 0$. In fact, if $\underline{A} = 0$, then there is an infinite series $\{s_n\}$ such that $A(t) > A(s_n)$ for $t \in [t_0 - \tau, s_n)$, $A'(s_n) \leq 0$ and $A(s_n) \to 0$ as $n \to \infty$. From (1.3), we have

$$m\left(1 + \frac{A(s_n)}{K}\right)A(s_n) \geq \frac{b}{2}\frac{1 + \mu(1 - \xi_0)r(s_n - \tau)}{1 + \mu r(s_n - \tau)}A(s_n - \tau).$$

As $A(s_n - \tau) > A(s_n)$, by using (2.1) we obtain

$$1 + \frac{A(s_n)}{K} > \frac{b}{2m}\frac{1 + \frac{2m\mu}{b}r(s_n - \tau)}{1 + \mu r(s_n - \tau)} = \frac{\frac{b}{2m} + \mu r(s_n - \tau)}{1 + \mu r(s_n - \tau)}.$$

Hence

$$\frac{A(s_n)}{K} > \frac{\frac{b}{2m} - 1}{1 + \mu r(s_n - \tau)} = \frac{b\xi_0}{2m[1 + \mu r(s_n - \tau)]} \geq \frac{b\xi_0}{2m(1 + \mu\bar{r})}$$

which clearly contradicts the assumption $A(s_n) \to 0$ and confirms $\underline{A} > 0$.

The remaining proof uses the same idea as in the proof of Theorem 2.1 based on the fluctuation lemma with a slightly more complicated calculation. Let $\{s_n\}$ be an infinite sequence with $A(s_n) \to \underline{A}$ and $A'(s_n) \to 0$ as $n \to \infty$. As $[1 + \mu(1 - \xi)x]/(1 + \mu x)$ decreases in $x \geq 0$, substituting $t = s_n$ in (1.3) leads to

$$m\left(1 + \frac{A(s_n)}{K}\right)A(s_n) \geq \frac{b}{2}\frac{1 + \mu(1 - \xi_0)\bar{r}}{1 + \mu\bar{r}}A(s_n - \tau) - A'(s_n).$$

By taking the infimum limit, we derive

$$m\left(1 + \frac{\underline{A}}{K}\right)\underline{A} \geq \frac{b}{2}\frac{1 + \mu(1 - \xi_0)\bar{r}}{1 + \mu\bar{r}}\underline{A}$$

and so

$$1 + \frac{\underline{A}}{K} \geq \frac{b}{2m}\frac{1 + \mu(1 - \xi_0)\bar{r}}{1 + \mu\bar{r}} = \frac{\frac{b}{2m} + \mu\bar{r}}{1 + \mu\bar{r}}.$$

It follows that

$$\underline{A} \geq K\left(\frac{\frac{b}{2m} + \mu\bar{r}}{1 + \mu\bar{r}} - 1\right) = K\frac{\frac{b}{2m} - 1}{1 + \mu\bar{r}} = \frac{bK\xi_0}{2m(1 + \mu\bar{r})}.$$

This completes the proof. $\qquad\square$

Suppose that one of the following three extreme conditions holds:

(1) $\xi = 0$ — *Wolbachia* infection does not modify the reproduction of wild *Aedes* mosquitoes at all.

(2) $\mu = 0$ — Wild female mosquitoes refuse to mate with released males completely.

(3) $R(t) \equiv 0$ — No males carrying a novel *Wolbachia* strain are released.

Then System (1.3) reduces to

$$\frac{dA(t)}{dt} = \frac{b}{2}A(t - \tau) - m\left(1 + \frac{A(t)}{K}\right)A(t), \tag{2.5}$$

which describes the dynamics of wild mosquito population without *Wolbachia* intervention. Theorem 2.1 applies to (2.5) with $\xi = 0$. Let A_0^* denote the constant in (2.2) in this case:

$$A_0^* = \frac{bK\xi_0}{2m} = \left(\frac{b}{2m} - 1\right)K. \tag{2.6}$$

Then Theorem 2.1 gives $\underline{A} \geq A_0^*$. Furthermore, by applying the proof of Theorem 2.1 in the last paragraph to the upper limit $\overline{A} = \limsup_{t\to\infty} A(t)$, we can also prove $\overline{A} \leq A_0^*$. It follows that $\overline{A} = \underline{A} = A_0^*$, and so $A(t) \equiv A_0^*$ is globally asymptotically stable as shown by Yu [25]. It indicates that A_0^* defines the carrying capacity of the wild adult mosquito population.

2.2. The lower bound for releasing

In view of Theorem 2.1 and the discussion following its proof, it is natural to assume

$$\mu > 0, \quad \xi > \xi_0, \quad r(t) > 0 \text{ for } t \geq t_0 - \tau, \tag{2.7}$$

in our search for the conditions ensuring the population suppression. When (2.7) holds,

$$r^* = \frac{b - 2m}{\mu[2m - b(1 - \xi)]} = \frac{\xi_0}{\mu(\xi - \xi_0)} > 0. \tag{2.8}$$

We show that r^* defines a lower bound for the releasing efforts, in the sense that if the supremum of $r(t)$ in $t \geq t_0 - \tau$ is below r^*, then $A(t)$ is bounded below by a positive constant. Corresponding to a constant release ratio $r(t) \equiv r$, (1.3) has an equilibrium point

$$A_r^* = \left(\frac{b}{2m} \cdot \frac{1 + \mu(1 - \xi)r}{1 + \mu r} - 1\right)K, \tag{2.9}$$

besides $A \equiv 0$. By comparing (2.6) and (2.9) we see that A_r^* reduces to A_0^* when $r = 0$, which confirms the consistency in the definitions (2.6) and (2.9). It is easy to check that A_r^* decreases in $r \geq 0$, which is positive for $r \in [0, r^*)$, vanishes uniquely at $r = r^*$, and becomes negative for $r > r^*$.

Theorem 2.3. *Let (2.7) hold. Suppose that* $\overline{r} = \sup_{[t_0-\tau,\infty)} r(t) < r^*$. *Then for each* $\phi \in C([t_0 - \tau, t_0], (0, \infty))$, *the solution* $A(t) = A(t, t_0, \phi)$ *of (1.3) satisfies*

$$0 < A_{\overline{r}}^* \leq \liminf_{t\to\infty} A(t) \leq \limsup_{t\to\infty} A(t) \leq A_{\underline{r}}^*, \tag{2.10}$$

where $\underline{r} = \inf_{[t_0-\tau,\infty)} r(t)$.

Proof. From the assumption $\bar{r} < r^*$ and the discussion on A_r^* before the statement of this theorem, we see that $A_{\bar{r}}^* > 0$. For an arbitrary positive number $a_1 < A_{\bar{r}}^*$ and $a_1 < \phi(t)$ on $[t_0 - \tau, t_0]$, we claim $A(t) > a_1$ for all $t \geq t_0$. Indeed, if this is not true, then we may let $t_1 > t_0$ be the least time at which $A = a_1$. Hence $A(t) > a_1$ in $[t_0, t_1)$, $A(t_1) = a_1$, and $A'(t_1) \leq 0$. Substituting $t = t_1$ into (1.3) leads to

$$
\begin{aligned}
m\left(1 + \frac{a_1}{K}\right)a_1 &\geq \frac{b}{2}\frac{1 + \mu(1-\xi)r(t_1 - \tau)}{1 + \mu r(t_1 - \tau)} A(t_1 - \tau) \\
&> \frac{b}{2}\frac{1 + \mu(1-\xi)\bar{r}}{1 + \mu\bar{r}} a_1.
\end{aligned}
$$

Consequently, we derive

$$
1 + \frac{a_1}{K} > \frac{b}{2m} \cdot \frac{1 + \mu(1-\xi)\bar{r}}{1 + \mu\bar{r}} \quad \Rightarrow \quad a_1 > \left(\frac{b}{2m} \cdot \frac{1 + \mu(1-\xi)\bar{r}}{1 + \mu\bar{r}} - 1\right)K = A_{\bar{r}}^*.
$$

This contradicts our assumption $a_1 < A_{\bar{r}}^*$ and establishes the claim. As a result, it also holds that the lower limit $\underline{A} \geq a_1$.

We use the fluctuation lemma again to complete the proof for the first part of (2.10). Let $\{s_n\}$ be an increasing and divergent sequence such that $A(s_n) \to \underline{A}$ and $A'(s_n) \to 0$ as $n \to \infty$. Replacing t by s_n in (1.3) gives

$$
m\left(1 + \frac{A(s_n)}{K}\right)A(s_n) \geq \frac{b}{2}\frac{1 + \mu(1-\xi)\bar{r}}{1 + \mu\,\bar{r}} A(s_n - \tau) - A'(s_n).
$$

By taking the infimum limit, we obtain

$$
m\left(1 + \frac{\underline{A}}{K}\right)\underline{A} \geq \frac{b}{2}\frac{1 + \mu(1-\xi)\bar{r}}{1 + \mu\,\bar{r}} \underline{A},
$$

from which a simplification of terms gives $\underline{A} \geq A_{\bar{r}}^*$.

As $\overline{A} \geq \underline{A} > 0$, we can use the fluctuation lemma directly to prove the second part of (2.10). Let $\{t_n\}$ be a divergent sequence such that $A(t_n) \to \overline{A}$ and $A'(t_n) \to 0$ as $n \to \infty$. Let $t = t_n$ in (1.3). We have

$$
m\left(1 + \frac{A(t_n)}{K}\right)A(t_n) \leq \frac{b}{2}\frac{1 + \mu(1-\xi)\underline{r}}{1 + \mu\,\underline{r}} A(t_n - \tau) - A'(t_n).
$$

By taking the supremum limit, we obtain

$$
m\left(1 + \frac{\overline{A}}{K}\right)\overline{A} \leq \frac{b}{2}\frac{1 + \mu(1-\xi)\underline{r}}{1 + \mu\,\underline{r}} \overline{A}.
$$

With a slight simplification, we find $\overline{A} \leq A_{\underline{r}}^*$ by the definition (2.9) of A_r^*. $\qquad \square$

When $r(t) \equiv r$ for a constant $r \in (0, r^*)$, an over-simplified assumption on the releasing efforts that the number of released males is proportional to the wild male number, we have $\bar{r} = \underline{r} = r$ and Theorem 2.3 implies $\lim_{t\to\infty} A(t) = A_r^* > 0$. It indicates that $A_{\bar{r}}^*$ and $A_{\underline{r}}^*$ probably provide the sharpest estimates for the lower and upper limits of $A(t)$.

2.3. The threshold release level for population suppression

We now prove that r^* sets a threshold level of infected male mosquito release for population suppression: As long as $r(t) \geq r^*$, the wild population will be eliminated ultimately. It indicates further that ξ_0 defines the threshold CI intensity over which a complete mosquito elimination is ascertained provided additionally that the release ratio $r(t) \geq r^*$.

Theorem 2.4. *Let (2.7) hold. Suppose there is $T > 0$ such that $r(t) \geq r^*$ for $t \geq T$. Then for any $\phi \in C([t_0 - \tau, t_0], (0, \infty))$, $\lim_{t \to \infty} A(t, t_0, \phi) = 0$.*

Proof. It suffices to show that the upper limit $\overline{A} = 0$. By the fluctuation lemma, there exists a divergent sequence $\{t_n\}$ such that $A(t_n) \to \overline{A}$ and $A'(t_n) \to 0$ as $n \to \infty$. When n is sufficiently large such that $t_n \geq T + \tau$, (1.3) gives

$$
\begin{aligned}
m\left(1 + \frac{A(t_n)}{K}\right) A(t_n) &= \frac{b}{2} \frac{1 + \mu(1 - \xi)r(t_n - \tau)}{1 + \mu\, r(t_n - \tau)} A(t_n - \tau) - A'(t_n) \\
&\leq \frac{b}{2} \frac{1 + \mu(1 - \xi)r^*}{1 + \mu\, r^*} A(t_n - \tau) - A'(t_n).
\end{aligned}
$$

Taking limit gives

$$
\begin{aligned}
m\left(1 + \frac{\overline{A}}{K}\right)\overline{A} &\leq \frac{b}{2} \frac{1 + \mu(1 - \xi)r^*}{1 + \mu\, r^*} \limsup_{n \to \infty} A(t_n - \tau) \\
&\leq \frac{b}{2} \frac{1 + \mu(1 - \xi)r^*}{1 + \mu\, r^*} \overline{A}.
\end{aligned}
$$

The inequality holds when $\overline{A} = 0$. If $\overline{A} > 0$, then

$$
m\left(1 + \frac{\overline{A}}{K}\right) \leq \frac{b}{2} \frac{1 + \mu(1 - \xi)r^*}{1 + \mu\, r^*} \quad \Rightarrow \quad \overline{A} \leq \left(\frac{b}{2m} \frac{1 + \mu(1 - \xi)r^*}{1 + \mu\, r^*} - 1\right)K = A^*_{r^*}
$$

by the definition of A^*_r in (2.9). However, as we have noticed that $A^*_{r^*} = 0$ right before the statement of Theorem 2.3, the last inequality leads to $\overline{A} \leq 0$ and a contradiction. Therefore, it must hold that $\overline{A} = 0$. $\square$

3. Further quantification of the hindrance by impaired mating competitiveness and CI

3.1. The dependence of the thresholds on parameters

In accordance with the basic assumptions (1.4), (2.1), and (2.7), the following condition will be maintained in the discussion below:

$$
b, \tau, K > 0; \quad m \in (0, 1); \quad \mu > 0; \quad \xi \in (0, 1]; \quad \xi_0 = 1 - \frac{2m}{b} > 0. \tag{3.1}
$$

In Theorems 2.1 – 2.4, we have identified ξ_0 as the threshold of the CI intensity, and

$$
r^* = r^*(\mu, \xi) = \frac{b - 2m}{\mu\,[2m - b(1 - \xi)]} = \frac{\xi_0}{\mu(\xi - \xi_0)} > 0 \tag{3.2}
$$

as the threshold for $r(t) = 2R(t)/A(t)$ – the ratio between the abundance $R(t)$ of released males infected by a novel *Wolbachia* strain absent in the natural population and the abundance $A(t)/2$ of wild male adults. As b/m can be interpreted as the net production rate of wild females, we see from (3.1) that *the threshold CI intensity ξ_0 is an increasing function of the natural reproduction rate of wild mosquitoes. If the infection does not induce complete CI and the CI intensity $\xi < \xi_0$, then the population suppression is improbable no matter how many infected males are released in the wild area.* If $\xi > \xi_0$ and for some $T > 0$, $r(t) \geq r^*$ for $t \geq T$, then the wild mosquito population will be eliminated ultimately. If $\bar{r} = \sup_{[t_0 - \tau, \infty)} r(t) < r^*$, then $A(t)$ is bounded below by the constant $A_{\bar{r}}^* > 0$ with

$$A_{\bar{r}}^* = \left(\frac{b}{2m} \cdot \frac{1 + \mu(1 - \xi)\bar{r}}{1 + \mu\bar{r}} - 1 \right) K$$

as defined in (2.9).

Our theorems are inclined to support a more important role of the CI intensity than the mating competitiveness μ in the population suppression. In contrary to the existence of the threshold CI intensity, our model does not generate a threshold level of μ. Since μ and the release ratio $r(t)$ appear together in two product forms of $\mu r(t - \tau)$, they relate reciprocally and a decrease in μ can be compensated by a propositional increase in $r(t - \tau)$. As shown in (3.2), the threshold release ratio r^* is reciprocal to each of μ and $\xi - \xi_0$. *The CI intensity ξ_0 not only warns an absolute failure of the population suppression when $\xi < \xi_0$, it also predicts a great challenge of mosquito control when ξ is not considerably higher than ξ_0.*
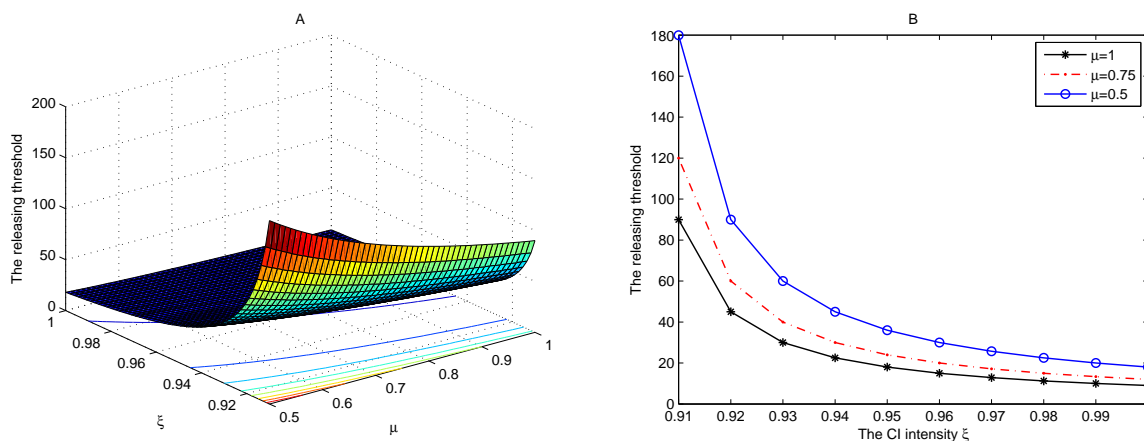

Figure 1. *The dependence of the threshold releasing ratio r^* on the CI intensity ξ and the mating competitiveness μ.* (A) r^* decreases in both $\xi \in [0.91, 1]$ and $\mu \in [0.5, 1]$ with the maximum $r^*(0.5, 0.91) = 180$ and the minimum $r^*(1, 1) = 9$. (B) For fixed $\mu = 0.5, 0.75, 1$, r^* has a relatively flat variation when the CI is close to be complete, but becomes very sensitive and increases sharply when ξ is close to the threshold intensity $\xi_0 = 0.9$.

For *Aedes albopictus* in Guangzhou, we have estimated $b \in [0.9043, 6.4594]$, $\tau \in [16, 66]$, and $m \in [0.0198, 0.1368]$ in [25], by combining the laboratory [32, 33, 34, 35] and field [27, 29, 34] data. To make our observations above more specific and transparent, we recall from our discussion on ξ and

μ in the introduction and fix

$$b = 2, \quad \mu \in [0.5, 1], \quad \xi \in [0.91, 1], \quad m = 0.1, \quad \tau = 19, \quad K = 20,000. \tag{3.3}$$

The constant K does not alter the CI intensity threshold ξ_0 or the release ratio threshold r^* and shows only a minimal impact on the dynamical behavior of $A(t)$. As it scales with the size of the studying area, we take $K = 20,000$ as a representative example. Clearly, the parameters in (3.3) satisfy (3.1) and determine $\xi_0 = 0.9$.

The dependence of r^* on $\xi \in [0.91, 1]$ and $\mu \in [0.5, 1]$ is shown in Figure 1A, and its dependence on ξ for fixed $\mu = 0.5, 0.75, 1$, is shown in Figure 1B. It decreases in both ξ and μ with the maximum value $r^*(0.5, 0.91) = 180$ and the least value $r^* = r^*(1, 1) = 9$. It indicates that for a complete elimination of wild *Aedes* mosquitoes, at least a ratio 9:1 of the released males over wild males needs to be maintained. Although it appears higher than the 5:1 ratio estimated in [25], the two different ratios do not contradict each other because the latter is estimated at the initial time with $r(0) = 5$ in a constant releasing policy with $R(t) \equiv R(0)$. As shown in Figure 1B, *the threshold ratio r^* is extremely sensitive to the CI intensity ξ when it is close to the threshold CI intensity level $\xi_0 = 0.9$.* Even with an equal mating competitiveness $\mu = 1$, a slight change from $\xi = 0.92$ to $\xi = 0.91$ doubles r^* from $r^*(1, 0.92) = 45$ to $r^*(1, 0.91) = 90$. On the other hand, when the CI is close to be complete, the change of r^* is relatively flat; e.g., $9 \le r^* \le 18$ for $\xi \in [0.95, 1]$ and $\mu = 1$.

3.2. The individual impacts on the suppression dynamics

We use numerical examples to demonstrate further that a reduction in the CI intensity ξ causes substantially higher damages than a reduction in the mating competitiveness μ in the population suppression. We compare the dynamical behavior of $A(t)$ with varying ξ or μ but fix the other parameter at 1. In the simulations, we use the same values for b, m, τ, and K as in (3.3). The environmental carrying capacity A_0^* determined by (2.6) equals $9K = 180,000$. For specificity, we also fix

$$\phi(t) = 20,000, \quad t \in [-19, 0], \quad r(t) \equiv 14. \tag{3.4}$$

The initial population size in the area is $1/9$ of the carrying capacity, while the releasing ratio is larger than the threshold value $r^*(1, 1) = 9$.

In Figure 2A, the mating competitiveness is fixed at $\mu = 1$ and the CI intensity decreases from 1 to 0.95 and 0.92. In agree with Theorem 2.4, $A(t) \to 0$ as $t \to \infty$ when $\xi = 1$. When ξ decreases to 0.95 or 0.92, a complete population suppression is impossible and Theorem 2.3 implies that $A(t) \to A_{14}^* \approx 2667$ and $A(t) \to A_{14}^* \approx 8267$, respectively, as $t \to \infty$. Although the wild population is not completely eliminated in the latter two cases, it is suppressed by $(180,000 - 2667)/180,000 \approx 98.52\%$ and $(180,000 - 8267)/180,000 \approx 95.41\%$ comparing to the steady-state (or the carrying capacity) of the wild population without *Wolbachia* intervention. In Figure 2B, $\xi = 1$ and μ decreases from 1 to 0.75 and 0.5. Interestingly, even when μ is decreased by 25% from 1 to 0.75, it still holds that $A(t) \to 0$ as $t \to \infty$. For $\mu = 0.5$, we have $A(t) \to A_{14}^* = 5000$ as $t \to \infty$. As $8267 > 5000$, we see that a slight decrease of the CI intensity from 1 to 0.92 is more devastating in the population suppression than halving the mating competitiveness from 1 to 0.5.
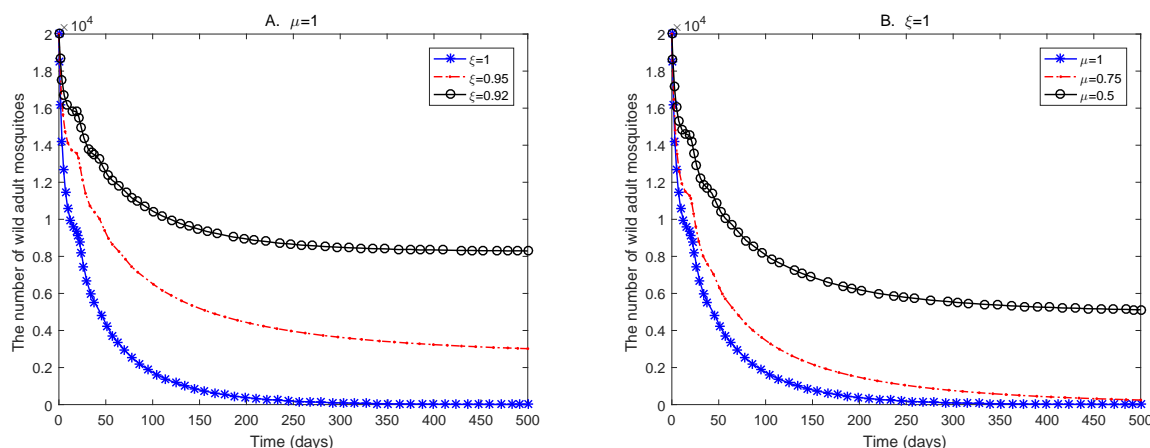
Figure 2. *The impacts of the CI intensity and the mating competitiveness on the suppression dynamics.* (A) With $\mu = 1$, the suppression succeeds when $\xi = 1$ but fails when ξ decreases slightly to 0.95 or 0.93. (B) With $\xi = 1$, the suppression succeeds when $\mu = 1$ and $\mu = 0.75$ and fails when $\mu = 0.5$. All other parameters are taken from (3.3) and (3.4).

3.3. Mosquito suppression during the peak season

Aedes albopictus in Guangzhou overwinters as diapause eggs with few surviving adults in open areas from December to February. With the elevation of temperature and precipitation in the spring, most diapause eggs start hatching at the turn of February to March. The adult population grows rapidly from the middle of March and reaches the first peak of the year in late May or early June [28, 29]. The population declines in the hot summer and bounces back to reach the second peak in September or October [26, 4]. The high-incidence season of dengue fever overlaps the second peak of mosquito abundance at the turn of September to October [36]. Breaking down the second peak of *Aedes* mosquitoes provides a temporary and efficient control of dengue transmission. Suppose we target at a more than 95% reduction of the adult mosquitoes on October 1 by a *Wolbachia* driven approach. When shall the infected male release be started? We note that a perfect answer to this question may not be reached easily as it involves many factors such as weather conditions, financial resource, labors, and the community support. In the remaining discussion, we use a numerical simulation based on our model to give a partial answer.

In the simulation, we use again the values for b, m, τ, and K specified in (3.3), which determine the carrying capacity $A_0^* = 180,000$. Set $t_0 = 0$ on March 1 before the burst of adult mosquito population and let $\phi(t) = 10,000$ on $[-19, 0]$. With the starting date on the first day of each month from March to September, we estimate the minimum constant releasing ratio and the corresponding number of released males such that the number of the wild adults on October 1 ($t \approx 210$) over the carrying capacity $180,000$ is less than 5%. For a given pair of $\mu > 0$ and $\xi \in [0, 1]$, we denote by $r = r_m(\mu, \xi)$ the minimum constant release ratio, and $\mathcal{N} = \mathcal{N}(\mu, \xi)$ the total number of released males. For $\mu = 0.75$ and $\xi = 1$, the temporal profiles of the wild adults interfered by infected male mosquitoes starting on different dates are shown in Figure 3A. We find $r_m = 41.8$ when the releasing starts on September 1, which reduces sharply to $r_m = 16.6$ when it starts one month early from August 1, and reduces moderately to $r_m = 11.8$ when it starts another month early on July 1. Very interestingly, we find that

the ratio r_m shows no significant reduction further when the starting date is shifted back to the first days of June, May, April, and March. These numbers seem to suggest that starting on August, about two months ahead of the target date, can be an optimal option for less financial and labor costs.
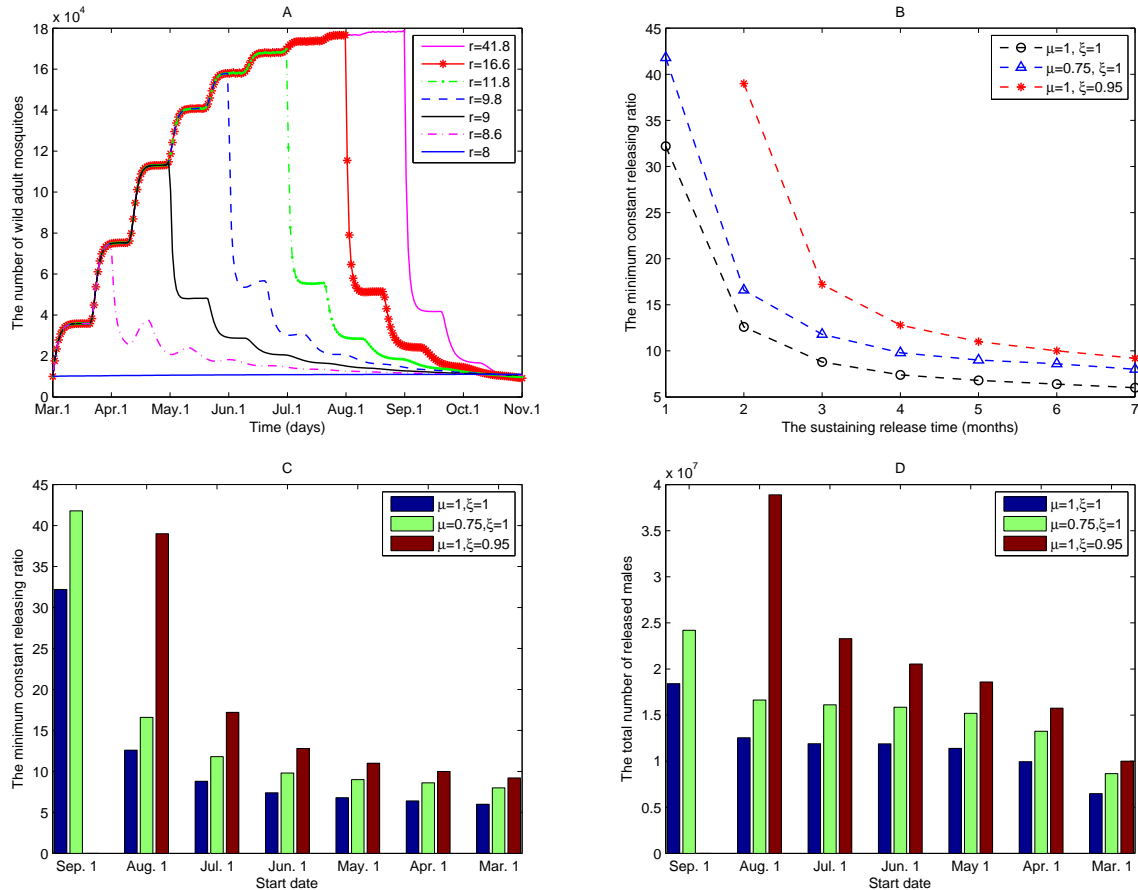

Figure 3. *Suppression of the wild Aedes albopictus population in the high-incidence season of dengue fever.* The parameters b, m, τ, and K are specified in (3.3); $t_0 = 0$ on March 1 and $\phi(t) = 10,000$ on $[-19, 0]$. (A) With $\mu = 0.75$, $\xi = 1$, the temporal profiles of the wild adults interfered by infected male mosquitoes at the indicated constant releasing ratios starting on the first days from March to September. (B) and (C) The minimum releasing ratios $r_m(\mu, \xi)$ for $(\mu, \xi) = (1, 1)$, $(0.75, 1)$, $(1, 0.95)$ in different starting dates for a more than 95% suppression of wild mosquitoes on October 1. (D) The total number $\mathcal{N}(\mu, \xi)$ of released males from different starting dates.

We examine further the variations of the minimum release ratio $r_m(\mu, \xi)$ and the total number $\mathcal{N}(\mu, \xi)$ on the starting dates for $(\mu, \xi) = (1, 1)$, $(0.75, 1)$, $(1, 0.95)$. The values of r_m are depicted in Figure 3B, C, and the values of $\mathcal{N}$ are depicted in Figure 3D; see also Table 1 where these numbers are listed. The variations of $r_m(1, 1)$, $\mathcal{N}(1, 1)$, and $\mathcal{N}(0.75, 1)$ on the starting dates all follow the same pattern as we discussed above for $(0.75, 1)$: A large reduction is seen when the date is moved from September 1 back to August 1, and only a moderate reduction is shown if the dates are moved back further. In addition, a 25% reduction in the mating competitiveness from $\mu = 1$ to $\mu = 0.75$ requires only a moderate

30% − 35% increase in the releasing amounts. In agree with our discussion in the previous section, a mild 5% reduction in the CI tensity from $\xi = 1$ to $\xi = 0.95$ causes more damages in the suppression than a 25% reduction in μ. The devastating impact is more obvious when the starting date is close to the target date October 1. For $(\mu, \xi) = (1, 0.95)$, our simulation reveals that it is nearly impossible to meet the suppression goal within one month: For a starting date on September 1, we find that even for the releasing ratio as high as $r = 10000, 16000, 20000$, the adult abundances on October 1 are still 7.39%, 7.33%, 7.20% over the carrying capacity. As shown in Table 1, $r_m(1, 095) = 39$ when the release starts on August 1, and reduces sharply to 17.2 if it starts on July 1, but shows no significant reduction in earlier starting dates. These numbers suggest an optimal starting date in July for male mosquito releasing in this case, other than August in the other two cases. *In summary, a loss in the CI intensity causes considerably more damages in the suppression of wild mosquito populations than the same magnitude of loss in the mating competitiveness. To reduce the adult population by more than 95% during the dengue fever peak season, an optimal starting date for infected male mosquito release is about three months ahead when the CI intensity is reduced by 5%. In a sharp contrast, when CI is complete, a two month implementation of the control measures is sufficient even if the mating competitiveness is reduced up to 25%.*

Table 1. *The minimum constant release ratio $r_m(\mu, \xi)$ and the total number $\mathcal{N}(\mu, \xi)$ of released males to reduce 95% of wild Aedes mosquitoes on October 1.* The parameters b, m, τ, and K are specified in (3.3); $t_0 = 0$ on March 1 and $\phi(t) = 10,000$ on $[-19, 0]$.

Start Date	$r_m(1, 1), \ \mathcal{N}(1, 1)$	$r_m(0.75, 1), \ \mathcal{N}(0.75, 1)$	$r_m(1, 0.95), \ \mathcal{N}(1, 0.95)$
Sept 1	32.2, 1.8409×10⁷	41.8, 2.4195×10⁷	
Aug 1	12.6, 1.2538×10⁷	16.6, 1.6635×10⁷	39, 3.8895×10⁷
July 1	8.8, 1.1896×10⁷	11.8, 1.6112×10⁷	17.2, 2.3286×10⁷
June 1	7.4, 1.1886×10⁷	9.8, 1.5848×10⁷	12.8, 2.0535×10⁷
May 1	6.8, 1.1395×10⁷	9, 1.5197×10⁷	11, 1.8596×10⁷
Apr 1	6.4, 0.9951×10⁷	8.6, 1.3249×10⁷	10, 1.5750×10⁷
Mar 1	6, 0.6489×10⁷	8, 0.8651×10⁷	9.2, 0.9996×10⁷

Conflict of interest

All authors declare no conflicts of interest in this paper.

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