Modelling the control of *Aedes albopictus* mosquitoes based on sterile males release techniques in a tropical environment

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ARTICLE INFO

ABSTRACT

The Sterile Insect Technique (SIT), used to control insect populations, consists of releasing males sterilized by ionizing radiations. Wild females that mate with these males can no longer produce viable offspring, which may drives the population decline. Although this method has proved its efficiency, its effect may be more limited for fast-reproducing large-population species, such *Aedes albopictus*. A novel approach, named "boosted SIT" has been designed to strengthen the SIT technique: It consists of coating sterile males with a biocide that will be transferred to the mated females, which will then contaminate the oviposition sites. This study is aimed at exploring demographic effects of both techniques (SIT and boosted SIT) through their inclusion in a weather-driven abundance model of the *Aedes albopictus* population dynamics in the geographical context of La Reunion Island. Sensitivity analysis showed that the date to start the release, as well as the quantity of sterile males released and their competitiveness, are of key importance for both control methods. According to our results, boosted SIT allows 1) Increasing the effectiveness of the SIT when the sterile males released are of medium quality in terms of competitiveness, and 2) extending the optimal window to start the control period.

1. Introduction

Vector-borne diseases account for about 17% of the estimated global burden of infectious diseases and are responsible for more than 700,000 deaths every year (World Health Organization and UNICEF, 2017). Dengue is the most common and widespread arbovirus. The number of dengue infections is estimated at 390 millions every year, of which 96 million induce clinical symptoms (of various severities) (Bhatt et al., 2013). Dengue virus is transmitted by mosquitoes of the genus *Aedes*, in particular *Ae. albopictus* and *Ae. aegypti*. These species are also vectors of other arboviruses, including Zika and Chikungunya. The global distributions of these three arboviruses have recently expanded, causing many severe disease outbreaks in urban human populations (Patterson et al., 2016). Different vaccines have been developed for dengue and Zika, but their efficacy remains to be studied (Musso and Gubler, 2016; WHO, 2018). Moreover, no disease-specific treatment for these arboviruses exists (Caglioti et al., 2013). In this context, mosquito control remains the cornerstone of disease prevention.

The "Tiger mosquito", *Aedes (Stegomyia) albopictus (Skuse) (Diptera: Culicidae)*, a species native to the forests of Southeast Asia (Smith, 1956), has expanded its distribution by adapting to new sources of blood and environments. Its proximity with humans has enabled it to colonize new territories through international trade (e.g. tire trade (Reiter, 1998)). Although being less competent than its sister species *Ae. aegypti* to transmit dengue viruses (Paupy et al., 2009), *Ae. albopicus* was the only vector involved in some recent dengue outbreaks (Gasperi et al., 2012; Paupy et al., 2009; Rezza, 2012; Wu et al., 2010).

For many mosquito-borne diseases, larvicides have demonstrated

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their efficiency to reduce transmission during outbreaks (World Health Organization, 2009). However, *Ae. albopictus* uses multiple cryptic and dispersed breeding sites of all sorts (tires, beverage cans, plastic items, etc.). They are difficult to locate and treat, which significantly hinders larvicides control of this vector (Connelly and Carlson, 2009). Mobilization of the local communities to eliminate these diverse containers used by peridomestic *Ae. albopictus* could be an effective solution, but changing attitudes and behaviors can take many years (Gubler and Clark, 1996; Tapia-Conyer et al., 2012; Winch et al., 1992). An integrated and sustainable control of *Ae. albopictus* is therefore necessary, which cannot rely solely on the usual insecticide usage or the goodwill of local communities, but must be supplemented by alternative treatment methods (Achee et al., 2019).

A promising alternative for such a cryptic-breeding insect is the Sterile Insect Technique (SIT). It relies on the mass-release of males sterilized by ionizing radiation. Since female mosquitoes are inseminated by only one male during their life (with very rare exceptions), mating with such males negates their reproductive success, hence causing the target population to decline (Dunn and Follett, 2017; Flores and O'Neill, 2018). SIT has been shown to be effective in eradicating tsetse flies (Vreysen et al., 2014), screwworms (Wyss, 2000) and medflies (Enkerlin et al., 2017). In the case of mosquito control, success has been more variable, although particularly good results have been obtained in Italy (Bellini et al., 2013) and more recently in China, in combination with the Incompatible Insect Technique (IIT) Zheng et al. (2019). Indeed, mosquito populations are generally very large, and a significant reduction in their population therefore requires the release of a large number of sterile males, whom breeding, sorting from females and irradiating are costly.

An efficacy-improving upgrade, named boosted SIT, has recently been proposed (Bouyer et al., 2016; Bouyer and Lefrançois, 2014): Its rationale is that the released males are the best available vectors to contaminate females with toxic agents that could be further disseminated to other compartments of the target population by self-dissemination. It has been proposed to coat the sterilized males with pyriproxyfen, an insect growth regulator that prevents the emergence of adult mosquito from the aquatic pupae (Invest and Lucas, 2008; Maoz et al., 2017): the insecticide could be transferred to females by mating, which in turn could specifically contaminate their breeding sites. By using females themselves as insecticide vectors, boosted SIT could therefore drastically improve control of species with cryptic breeding habits such as *Ae. albopictus*. However, many questions remain, such as the number of males to be released for efficient control, or the magnitude of the potential "boosting" effect. Both depend on the duration of contamination of breeding sites (no consensus appears in the bibliography (Invest and Lucas, 2008)) and on the effectiveness of pyriproxyfen transfers from males to females and from females to breeding sites, parameters for which empirical data are not available yet.

In cases empirical data are lacking, mathematical models are often useful for planning mosquito population management strategies. They can be used to understand and predict population density in relation to environmental variations (Ewing et al., 2016; Ezanno et al., 2015; Roche et al., 2015; Tran et al., 2013), and to anticipate the effects of population management measures under various scenarios (Cailly et al., 2012). In the case of SIT, such theoretical models have been developed in order to 1) optimize the strategies of sterile males releases (Almeida et al., 2019; Cai et al., 2014; Evans and Bishop, 2014; Huang et al., 2017; Li and Yuan, 2015; Multerer et al., 2019; White et al., 2010), 2) study the impact of the environment on SIT (Dufourd and Dumont, 2013; Maiti et al., 2006; Mishra et al., 2018), and 3) evaluate the effect of SIT coupled with standard use of insecticides (Fister et al., 2013; Hendron and Bonsall, 2016). A recently-published model by Pleydell and Bouyer (2019) specifically studied the efficacy gain of boosted *versus* standard SIT in a theoretical population. Their results suggest that boosted SIT could drastically reduce the required number of males released. However, to our knowledge, none of these models have studied the effects of SIT or boosted SIT on *Ae. albopictus* populations under realistic environmental conditions.

The objectives of the present study were thus 1) to evaluate the efficacy gain of boosted SIT in real geographical and climatic conditions, with the example of La Reunion Island a tropical island where *Ae. albopictus* is the main chikungunya and dengue vector (Delatte et al., 2008), and 2) to optimize SIT and boosted SIT strategies in this context. Between 2005 and 2006, Reunion Island was affected by a large chikungunya epidemic, with more than 38% of the population infected (ARS and IVS, 2010). An epidemic of dengue is currently spreading, with more than 24,300 indigenous cases as of July 01, 2019 (ARS and Préfecture Réunion, 2019). Located in the Indian Ocean, between Madagascar and Mauritius, La Reunion Island is a small volcanic island (2512 km^2) with a mountainous topography. *Aedes albopictus* mosquitoes are mainly found at low elevations in urban and peri-urban areas (Boyer et al., 2014). Moreover, the island is characterized by an East/West precipitation gradient, ranging from a maximal annual rainfall of 15,931 mm recorded in the eastern part, to a minimal annual rainfall of 183 mm in the West (Météo France, 2019). The island is characterized by two seasons, with a hot and wet austral summer (from November to March), and a rather mild and dry winter. La Reunion Island, with its diverse landscapes and contrasting climate, is thus an excellent place to study the impact of control methods against *Ae. albopictus* in a realistic, variable, environment. Moreover, since the severe 2005–2006 chikungunya epidemic, *Ae. albopictus* populations have been regularly monitored by the Regional Health Agency. A deterministic model of *Ae. albopictus* population dynamics has been recently developed by Tran et al. (2020) and validated using these extensive entomological data. This model realistically integrates the climatic variations of La Reunion Island on the *Ae. albopictus* population dynamics (Tran et al., 2013): i) Temperature impacts the development time of aquatic stages and the mortality of larvae, pupae and adults, ii) rainfalls positively impact the number of available breeding sites and the environmental carrying capacity, iii) heavy rainfalls impact the mortality rates of aquatic stages by flooding the breeding habitats (Dieng et al., 2012). This model is currently used by the Regional Health Agency as a tool for decision support, called "ALBORUN" (Tran et al., 2020).

In the present study, we modified this ALBORUN population dynamic model to integrate the potential effects of SIT and boosted SIT on the *Ae. albopictus* populations in La Reunion Island. After controlling its accuracy on the same entomological data used in Tran et al. (2020), we first performed a global sensitivity analysis to identify the key parameters affecting the efficacy of SIT and boosted SIT. We then assessed the optimal timing for both control methods under a tropical environment, taking into account the spatial heterogeneity of micro-climates in La Reunion Island to produce a detailed map of the locally-optimal starting months of the control period. Finally, we studied the effects of two different sterile males release strategies, constant or density-dependent, on *Ae. albopictus* populations.

2. Materials and methods

2.1. Study area

The study area is delimited by 1203 operational urban sectors defined by the vector control service of the Regional Health Agency. 31 weather stations of the French Meteorological Service at La Reunion Island provide the daily average temperature and rainfall intensity records from 2011 to 2016. Each operational urban sector is associated with the nearest weather station (Fig. 1).

2.2. Weather-driven abundance model

To simulate *Ae. albopictus* population dynamics, we modified the ALBORUN mechanistic model (Tran et al., 2020). ALBORUN computes the densities of the different stages of *Ae. albopictus* life cycle, aquatic
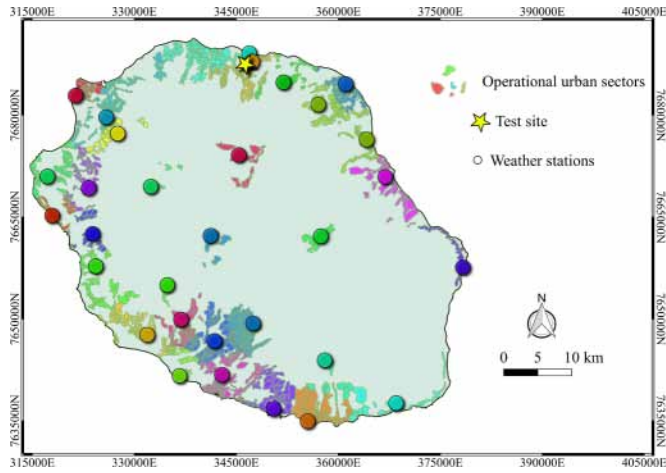
Fig. 1. Map of La Reunion Island with the localization of operational urban sectors (defined by the Regional Health Agency) and their associated weather stations (from the French meteorological service), in matching colors. The star is the location of the Duparc sector, where sterile male release trials started in July 2019..

(eggs: E, larvae: L, pupae: P) and aerial (emerging females: F_{em}, nulliparous females: F_n, parous females: F_P), using a system of ordinary differential equations (ODE). Parous females are females that have taken a blood meal and oviposited at least once, whereas nulliparous females did not yet lay eggs. Nulliparous and parous females are both again divided into three compartments according to the gonotrophic cycle, distinguishing between host-seeking females, engorged females and females seeking a breeding site. In total, the model is composed of 10 compartments. It thus makes it possible to compute independently and simultaneously the population dynamics in each operational urban sector. The ALBORUN outputs have been validated using entomological field data from La Reunion Island (Tran et al., 2020).

In the present study, ALBORUN was modified to assess effects of SIT and boosted-SIT control strategies (Fig. 2):

1. As these strategies are based on the release of sterile males, a specific male compartment M was explicitly included; it computes the number of wild males available for mating with females;
2. The number of compartments was reduced to avoid over-parametrization. The sub-compartments for nulliparous and parous females were thus aggregated into a single compartment each (nulliparous females: F_n, parous females: F_P).

The modified model, called "mALBORUN", is therefore:

$$\begin{cases} \dfrac{dE}{dt} = f_F(\beta_1 F_n + \beta_2 F_p) - (m_E + f_E)E \\[2mm] \dfrac{dL}{dt} = f_E E - \left(m_L\left(1 + \dfrac{L}{K_L}\right) + f_L\right)L \\[2mm] \dfrac{dP}{dt} = f_L L - (m_P + f_P)P \\[2mm] \dfrac{dF_{em}}{dt} = \sigma f_P P \exp\left(-\mu_{em}\left(1 + \dfrac{P}{K_P}\right)\right) - (m_{F_{em}} + \gamma_{F_{em}})F_{em} \\[2mm] \dfrac{dF_n}{dt} = \gamma_{F_{em}} F_{em} - (m_F + \mu_{F_r} + f_F)F_n \\[2mm] \dfrac{dF_p}{dt} = f_F F_n - (m_F + \mu_{F_r})F_p \\[2mm] \dfrac{dM}{dt} = (1 - \sigma)f_P P \exp\left(-\mu_{em}\left(1 + \dfrac{P}{K_P}\right)\right) - \mu_M M \end{cases}$$

$$(1)$$

The Greek letters represent parameters that are not influenced by weather: β_1 and β_2 respectively represent the egg laying rate of

nulliparous and parous females, σ is the sex-ratio, $\gamma_{F_{em}}$ is the rate of emerging females that succeed in blood feeding (thus becoming gravid but still nulliparous females, as they have not completed a full gonotrophic cycle). f_F correspond to the transition rate from nulliparous to parous females. μ_{em} is the pupae mortality rate at emergence, *i.e.* the transition from pupae to emerging adults, and μ_{F_r} corresponds to the additional mortality rate during breeding-site seeking behavior. The Arabic letters are weather-driven functions: f_x is the transition rate from stage x to the next, m_x is the mortality rate at stage x, and K_L and K_P are the breeding-sites carrying capacity for larvae and pupae, respectively. In the aquatic stage, larval and pupal competition are modeled by two density-dependant functions modifying their mortality rate. The pupal competition occurs at emergence: As the emergence time is short (Clements, 2000), the classic formula of density-dependent survival rate $\left(1 - \mu_{em}\left(1 + \dfrac{P}{K_P}\right)\right)$, meaning that the competition induces a higher death rate at emergence when pupae density P increases, can be expressed as a probability rate using the formula $\exp\left(-\mu_{em}\left(1 + \dfrac{P}{K_P}\right)\right)$ (Cailly et al., 2012). Larval mortality (m_L) is similarly increased when their density L increases. Parameters and functions are similar to the ALBORUN model by Tran et al. (2020) (Table: 1).

Due to the aggregation of female sub-compartments, the value of the parameter μ_{F_r} and the function f_F had to be reevaluated to ensure consistency between the original and modified models. The value of μ_{F_r} was estimated using a maximum likelihood method ("Multi-Level Single-Linkage" or MLSL algorithm, nloptr package, R software, https://cran.r-project.org/web/packages/nloptr/index.html) to adjust mALBORUN to the outputs of ALBORUN (*i.e.* the density of mosquitoes for each compartment). In addition, the mALBORUN f_F value was obtained by summing the times spent by the nulliparous and parous females in the host-seeking, blood-feeding and breeding site-seeking compartments in ALBORUN.

For each time step, mALBORUN predicts the abundance of *Ae. albopictus* for the seven stages and for each operational urban sectors. The model was further validated using the entomological data from Tran et al. (2020), *i.e.* a longitudinal study on the larval stages of *Ae. albopictus* at five northern sites in 2012 and 2013 A Spearman test was performed to assess the correlation coefficient between the observed larvae abundances and those predicted by the model.

2.3. Modelling the effects of control methods

2.3.1. SIT model

mALBORUN (Eq. 1, Fig. 2) was then extended to include the effects of sterile male releases for the SIT control method (mALBORUN-SIT model, Fig. 3). The ODE thus becomes:
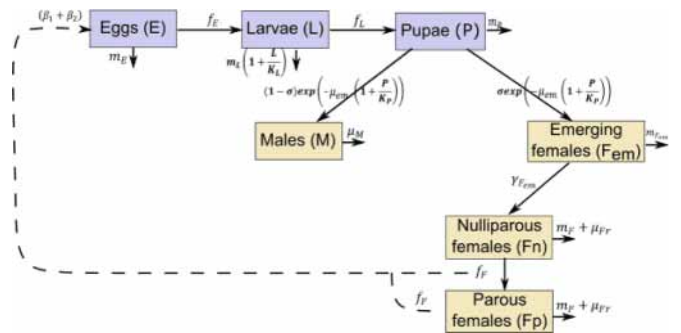

Fig. 2. Diagram of the modified weather-driven abundance model. *The compartments in blue correspond to the aquatic stages, those in yellow correspond to the aerial stages.*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
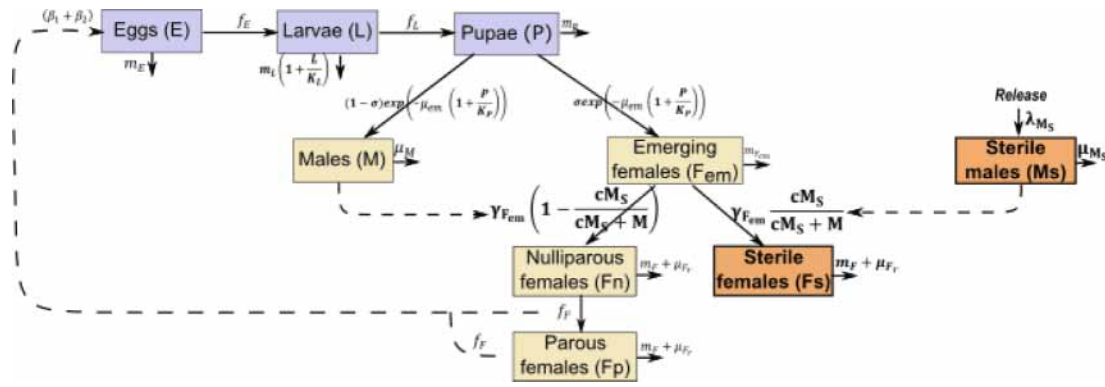
Fig. 3. Diagram of the mALBORUN-SIT model. *The bolded and orange compartments are the compartments that have been added to mALBORUN (Fig. 2).*

$$
\begin{cases}
\dfrac{dE}{dt} = f_F(\beta_1 F_n + \beta_2 F_p) - (m_E + f_E)E \\[2mm]
\dfrac{dL}{dt} = f_E E - \left(m_L\left(1 + \dfrac{L}{K_L}\right) + f_L\right)L \\[2mm]
\dfrac{dP}{dt} = f_L L - (m_P + f_P)P \\[2mm]
\dfrac{dF_{em}}{dt} = \sigma f_P P exp\left(-\mu_{em}\left(1 + \dfrac{P}{K_P}\right)\right) - (m_{F_{em}} + \gamma_{F_{em}})F_{em} \\[2mm]
\dfrac{dF_n}{dt} = \gamma_{F_{em}}F_{em}\left(\boldsymbol{1 - \dfrac{cM_s}{cM_s + M}}\right) - (m_F + \mu_{F_r} + f_F)F_n \\[2mm]
\dfrac{dF_p}{dt} = f_F F_n - (m_F + \mu_{F_r})F_p \\[2mm]
\boldsymbol{\dfrac{dF_s}{dt} = \gamma_{F_{em}}F_{em}\dfrac{cM_s}{cM_s + M} - (m_F + \mu_{F_r})F_s} \\[2mm]
\dfrac{dM}{dt} = (1 - \sigma)f_P P exp\left(-\mu_{em}\left(1 + \dfrac{P}{K_P}\right)\right) - \mu_M M \\[2mm]
\boldsymbol{\dfrac{dM_s}{dt} = -\mu_{M_s}M_s} \\[2mm]
M_s(T_{start} + n\tau^+) = M_s(T_{start} + n\tau) + \lambda_{M_s}, \qquad \boldsymbol{n = 1, 2, 3.}
\end{cases}
\tag{2}
$$

where the equations that are different from mALBORUN (Eq. 1) are bolded. M_s is the abundance of sterile males in the population. The simulated SIT control period starts at date T_{start}, and a number λ_{M_s} of

males sterilized by radiation is released periodically (which increases M_s); τ and n are the periodicity and number of releases, respectively, $n\tau^+$ is the moment immediately after the nth release. The irradiation affects the mortality μ_{M_s} of the sterile males (Balestrino et al., 2010; Oliva et al., 2013). It also has an impact on their competitiveness c, which summarizes the ability of sterile males to find females, mate and transfer semen, as well as the number of females with whom they are able to copulate with Oliva et al. (2012); c is expressed relatively to wild males, *i.e.* $0 \leq c < 1$ when sterile males M_s are less competitive than their wild counterparts M, $c = 1$ when they are similar. In the case where encounting leads to mating, and since females can only be fertilized once, their spermatheca are filled with sterile sperm. Thus, $F_{em}\dfrac{cM_s}{cM_s + M}$ females become sterilized females F_s (*i.e.* they cannot produce viable offspring; (Anguelov et al., 2012; Esteva and Mo Yang, 2005; Mishra et al., 2018; Thome et al., 2010)

For emerging females F_{em}, $p = \dfrac{cM_s}{cM_s + M}$ is the probability to mate a sterile male and (1-p) is the probability to mate with a wild male. Females that mate with sterile or wild males become either sterile or nulliparous, with a transition rate .

2.3.2. Boosted SIT model

mALBORUN-SIT model (Eq. 2, Fig. 3) was then extended to incorporate the boosted SIT effects (mALBORUN-BSIT model, Fig. 4) and
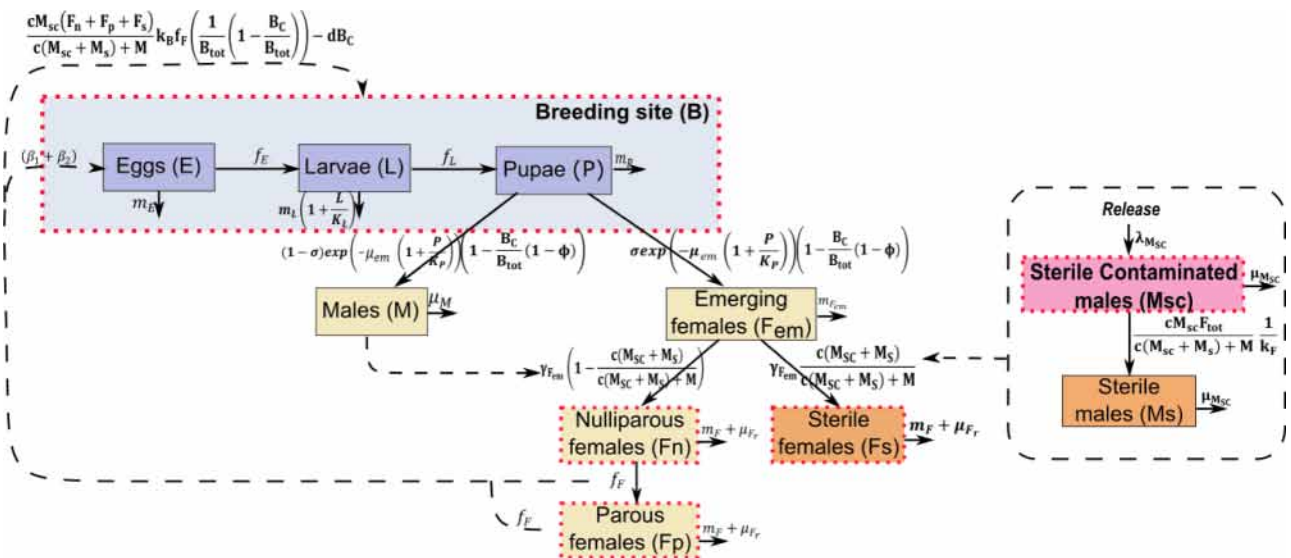

Fig. 4. Diagram of the mALBORUN-BSIT model. *The bolded compartments have been added to mALBORUN-SIT. The red-dashed compartments are those that can be contaminated by the pyriproxyfen.*

the ODE becomes:

$$
\begin{cases}
\dfrac{dE}{dt} = f_F\,(\beta_1 F_n + \beta_2 F_p) - (m_E + f_E)E \\[8pt]
\dfrac{dL}{dt} = f_E E - \left(m_L(1 + \dfrac{L}{K_L}) + f_L\right)L \\[8pt]
\dfrac{dP}{dt} = f_L L - (m_P + f_P)P \\[8pt]
\dfrac{dF_{em}}{dt} = \sigma f_P P \exp\left(-\mu_{em}(1 + \dfrac{P}{K_P})\right)\left(\boldsymbol{1 - \dfrac{B_c}{B_{tot}}(1 - \phi)}\right) - (m_{Fem} + \gamma_{Fem})F_{em} \\[8pt]
\dfrac{dF_n}{dt} = \gamma_{Fem}F_{em}\left(1 - \dfrac{c(\boldsymbol{M_{sc}}+M_s)}{c(\boldsymbol{M_{sc}}+M_s) + M}\right) - (m_F + \mu_{F_r} + f_F)F_n \\[8pt]
\dfrac{dF_p}{dt} = f_F F_n - (m_F + \mu_{F_r})F_p \\[8pt]
\dfrac{dF_s}{dt} = \gamma_{Fem}F_{em}\dfrac{c(\boldsymbol{M_{sc}}+M_s)}{c(\boldsymbol{M_{sc}}+M_s) + M} - (m_F + \mu_{F_r})F_s \\[8pt]
\dfrac{dM}{dt} = (1 - \sigma)f_P P \exp\left(-\mu_{em}(1 + \dfrac{P}{K_P})\right)\left(\boldsymbol{1 - \dfrac{B_c}{B_{tot}}(1 - \phi)}\right) - \mu_M M \\[8pt]
\boldsymbol{\dfrac{dM_{sc}}{dt} = -\dfrac{M_{sc}F_{tot}}{c(M_{sc} + M_s) + M}\dfrac{1}{k_F} - \mu_{M_{sc}}M_{sc}} \\[8pt]
\dfrac{dM_s}{dt} = \dfrac{M_{sc}F_{tot}}{c(M_{sc} + M_s) + M}\dfrac{1}{k_F} - \mu_{M_{sc}}M_s \\[8pt]
\boldsymbol{\dfrac{dB_c}{dt} = \dfrac{cM_{sc}(F_n + F_p + F_s)}{c(M_{sc} + M_s) + M}k_B f_F\left(1 - \dfrac{B_c}{B_{tot}}\right) - dB_c} \\[8pt]
\boldsymbol{M_{sc}(T_{start} + n\tau^+) = M_{sc}(T_{start} + n\tau) + \lambda_{M_{sc}}, \qquad n = 1, 2, 3.}
\end{cases}
$$

$$\tag{3}$$

where the equations that are different from mALBORUN-SIT (Eq. 2) appear in bold.

The objective of the boosted SIT is to impact the emergence of *Ae. albopictus* via the pyriproxyfen through the contamination of breeding sites. We therefore introduced B_{tot} the total number of breeding sites, and B_c, the number of contaminated breeding sites. In uncontaminated breeding sites (probability $1 - \dfrac{B_c}{B_{tot}}$) F_{em} females and M males would emerge from pupae at the same rate as in the mALBORUN-SIT model. However, this rate may be lower in contaminated breeding sites (probability $\dfrac{B_c}{B_{tot}}$), as emergence is inhibited by pyriproxyfen. Let ϕ be the proportion of adults emerging from pupae in pyriproxyfen-contaminated sites, the overall emergence rate would therefore be modified by the factor $1 - \dfrac{B_c}{B_{tot}}(1 - \phi)$. When $\phi = 0$ the effect of pyriproxyfen is maximal: no pupae can emerge from a contaminated breeding site ; conversely, when $\phi = 1$, all pupae can emerge despite the presence of pyriproxyfen (e.g. resistance of *Aedes albopictus* to pyriproxyfen), which is equivalent to SIT alone (Fig. G1).

For this strategy, the released males are always sterile, but they are also coated with pyriproxyfen; their abundance is noted M_{sc}. During the control period with the boosted SIT, a number $\lambda_{M_{sc}}$ of these males is periodically released in the population (the periodicity τ and the number of releases n can be modified, see mALBORUN-SIT model). When mating with females, M_{sc} males transfer part of their pyriproxyfen coating to the females, thus contaminate them, the "boosting" effect being that these females would in turn contaminate the breeding sites B_c. This transfer results in these males loosing their coating, thus becoming "sterile-uncontaminated males" M_s. Since M_{sc} males can mate with any females in the population, the number of contacts is $\dfrac{cM_{sc}F_{tot}}{c(M_{sc} + M_s) + M}$, where $F_{tot} = F_{em} + F_n + F_p + F_s$ (i.e. the total number of adult females), and c the competitiveness of irradiated males (whether M_{sc} or M_s, see mALBORUN-SIT model). The number of M_{sc} becoming sterile-uncontaminated males M_s is therefore $\dfrac{cM_{sc}F_{tot}}{c(M_{sc} + M_s) + M}\dfrac{1}{k_F}$, where k_F allows to adjust the number of mates necessary for the M_{sc} males to lose their coating. However, all released males, whether still coated with pyriproxyfen (M_{sc}) or having lost their coating (M_s), are sterile, and can therefore sterilize females.

As in mALBORUN-SIT, the reproductive status of emerging females F_{em} in mALBORUN-BSIT will be determined by their first mating: if they mate with a sterile male (probability $p = \dfrac{c(M_{sc} + M_s)}{c(M_{sc} + M_s) + M}$, they become sterile females F_s, if they mate with a wild male (probability $1 - p$), they become nulliparous gravid females F_n.

In order to limit the number of compartments, we did not make an explicit distinction between contaminated and uncontaminated females. Any female can be contaminated by M_{sc} males: emerging F_{em}, nulliparous F_n, parous F_p or sterile F_s, even if the last three categories cannot be fecundated. As F_{em} females become F_s after such mating, $\dfrac{cM_{sc}(F_n + F_p + F_s)}{c(M_{sc} + M_s) + M}$ is the number of females contaminated with pyriproxyfen after contact with M_{sc} males. We thus considered that any mated females (sterile or not) oviposit in larval breeding sites after a time f_F. If they were contaminated, they would then transfer some of their pyriproxyfen to breeding sites, thus reducing their level of contamination until complete decontamination. This imperfect transfer of pyriproxyfen transfer is modelled by the factor k_B, the number of females required to contaminate a breeding site. When $0 \leq k_B < 1$, several females are required to contaminate a single breeding site (imperfect transfer of pyriproxyfen from M_{sc} males to females, rapid decontamination of females, insufficient transfer of pyriproxyfen to the breeding site, ...). When $k_B > 1$, a single female can contaminate several breeding sites. Overall, $\dfrac{cM_{sc}(F_n + F_p + F_s)}{c(M_{sc} + M_s) + M}k_B f_F$ is therefore the "effective" number of contaminated breeding sites.

To compute the number of new contaminated breeding site, we also considered the probability that a breeding site was not yet contaminated, i.e. $1 - \dfrac{B_c}{B_{tot}}$. Finally, we took into account the possibility that a breeding site B_c may remain contaminated for only a limited period of time d.

2.3.3. Models outputs

At each time-step, the models predict the abundance of *Ae. albopictus* for each stage and for each operational urban sector. Moreover, four synthetic model outputs were computed to assess the impact of both SIT and boosted SIT methods on the mosquito population (Fig. A1):

1. the *reduction rate* was calculated as the size of females ($F_n + F_p$) during the control period divided by i) the size of females without control, to evaluate the effect of the SIT, and ii) the size of females during the SIT control, to evaluate the added effect of the boosted SIT.
2. the *sterility rate* was defined as the number of sterile females F_s divided by the total number of fertilized females ($F_n + F_p + F_s$) during the control period.
3. the *resilience* corresponds to the time required to return to the natural dynamics. It was calculated as the number of days required after a treatment period for the controlled population to reach the same abundance as a uncontrolled population.
4. the *reduction of emergence* was estimated as the ratio between the number of pupae present in contaminated breeding sites that became adults during the boosted SIT control and the number of pupae that became adults in a similar but uncontrolled population

2.3.4. Sensitivity analysis

A Sensitivity Analysis (SA) was performed on the four synthetic outputs using the variance-based method of Fourier Amplitude Sensitivity Test Saltelli et al. (2000) with the Sensitivity R package (https://cran.r-project.org/web/packages/sensitivity/index.html). The parameters of mALBORUN-SIT (μ_{M_s}, c), mALBORUN-BSIT ($\mu_{M_{sc}}$, d, k_F, k_B) and the parameters relative to the release (τ, n, T_{Start}, λ_{M_s}, $\lambda_{M_{sc}}$) were

varied simultaneously using a uniform distribution. The boundaries of the parameters were chosen according to knowledge from bibliography, results of experiments and observational studies (Table: 2). The parameters contributing to more than 20% of the variance of a given model output were considered to have a strong influence on the output. The SA was replicated on four urban sectors selected randomly in the North, South, East and West of the island to account for environmental variability. Model sensitivity was analyzed over 256,000 simulations. Only outputs with normally distributed variations were analyzed.

2.3.5. Release strategies
Release starting month:

We produced a map of the optimal release starting month for each output of mALBORUN-SIT and mALBORUN-BSIT model. The release starting date (T_{start}) varied from January to December. The optimal release starting month corresponds to the month for which the output values is maximum. Due to the inter-annual weather variations, the simulations were replicated for three years (2013, 2014, 2015), and since several operational urban sectors are connected to the same weather station, the simulations were computed for only one sector per weather station, selected randomly.

We have also performed an optimization in order to find the month that gives the best value for all model outputs to summarize information in only one map. For this purpose, we defined the function:

$f(T_{Start}, s)$

$$= -\sum_y (\text{Reduction rate}_y + \text{Sterility rate}_y + \frac{\text{Resilience}_y}{365} + \text{Emergence reduction}_y)$$

$$\text{with} \quad \begin{cases} s \in \text{urban sectors} \\ y \in [2013; 2015] \end{cases}$$

(4)

The higher the values of all outputs of the models (*i.e.* in terms of *Ae. albopictus* populations control) for a given starting date (T_{Start}) and urban sector (*s*), the lower the value of the function $f(T_{Start}, s)$. It should be noted that the resilience was divided by 365 days, so that any effect lasting more than one year had a strong influence. A global and local optimization algorithm from the nloptr R package (https://cran.r-project.org/web/packages/nloptr/index.html)) was then used to minimize the function $f(T_{Start}, s)$.

Number of sterile male released:

Two strategies differing in the number of sterile male released each time (mALBORUN-SIT: λ_{M_s}, mALBORUN-BSIT: $\lambda_{M_{sc}}$) were compared:

1. In the first strategy, both λ_{M_s}, $\lambda_{M_{sc}}$ and τ were constant during the control period. Ten λ_{M_s} and $\lambda_{M_{sc}}$ values were tested from 1, to 10 times the sum of nulliparous and parous females at the beginning of the control period; six τ were tested, from 15 days down to 5. A total of 60 simulations were performed for an extended release control period of three or six month.

2. In the second strategy, λ_{M_s} and $\lambda_{M_{sc}}$ values were proportional to the number of nulliparous and parous females at the release dates. The values of λ_{M_s}, $\lambda_{M_{sc}}$, τ, and the total number of simulations were similar to the first strategy.

The SIT program has chosen one site for the their future sterile male release trials corresponding to one of the operational urban sectors in Reunion Island called "Duparc Sector" (Fig. 1). We therefore selected this site to predict the impact of the two different release strategies on the control of the local population of *Ae. albopictus*, for both SIT and boosted-SIT methods.

2.4. Initialization and simulations

Models were implemented in R (http://www.rproject.org/). At $t = 0$, the population consisted in 1000 eggs for each operational urban sectors. Simulations ran over 6 years. We used the weather data from 2011 to 2016 as the input of the models. The first year was not retained for outputs computation. No sterile male has been released during the last year, which allowed computing the time required for the *Ae. albopictus* population to recover its natural dynamics, *i.e.* the resilience time (in days).

3. Results

The ALBORUN model has been modified and simplified, in order to model the effects of control methods (mALBORUN). As in the original model, mALBORUN predicts the abundances of *Ae. albopictus* by stage (eggs, larvae, pupae, adults: females and males) over time for each operational urban sector, using daily rainfall and temperature data over 6 consecutive years as entries. The effects of the SIT (mALBORUN-SIT) and boosted SIT (mALBORUN-BSIT) were then introduced to predict and compare the impact of the two control strategies under different scenarios (Fig. 5).

3.1. mALBORUN is consistent with the entomological data

Simulated mosquito abundances of the modified mALBORUN model, based on weather conditions, are consistent with the entomological data collected at five locations in 2012 and 2013 in La Reunion Island (Fig. 6). As in the original ALBORUN model (Tran et al., 2020), the predictions were strongly correlated with the observed abundances (P-value < 0.001) at sites with higher larval densities and high seasonal variations (correlation coefficients for Saint-Paul: 0.86; La Possession: 0.70; Sainte-Marie: 0.68; Sainte-Suzanne: 0.75). The correlation coefficient was lower (0.61, P-value= 0.06) for the eastern site (St-Benoit), where the observed abundances of *Ae. albopictus* was lower (< 20 larvae/trap) with few seasonal variations. Nevertheless, the model reproduced the major trends in the intra-annual population fluctuations for all sites: abundances indeed show a peak occurring in March-April, at the end of the austral summer, and a minimum at the end of the austral winter (Fig. 5).
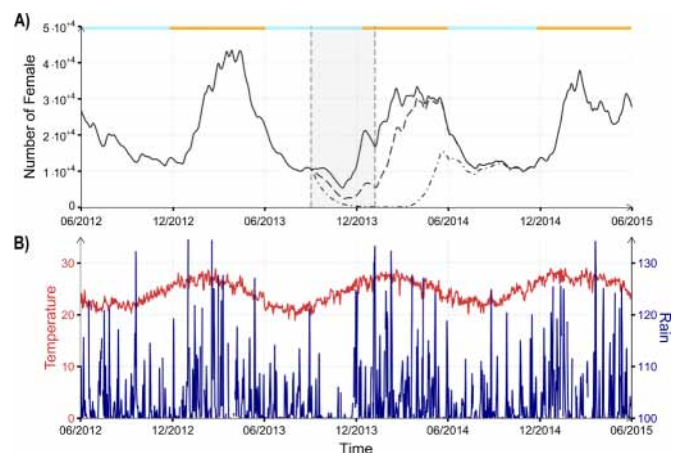

Fig. 5. Predicted adult females of *Aedes albopictus* population in La Reunion Island *A) Simulated number of adult females (nulliparous (F_n) + parous (F_p)) and B) Daily rainfall (blue) and mean temperature (red) in the Duparc Sector. Population dynamics without control (mALBORUN) is represented in solid line and the population dynamics controlled with SIT (mALBORUN-SIT) and boosted SIT (mALBORUN-BSIT) are represented in long dashed line and in dotted line respectively. The grey background indicates the control period and the colored bars symbolize in orange the austral summer (November-March) and in light blue the austral winter on the top panel. Parameter values and functions of the models are in Tables 1 and 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)*

Table 1

Parameters value and functions for ALBORUN (Tran et al., 2020) *The letter R and T correspond to the daily rainfall and temperature respectively.*

Parameters	Definition	Value	Ref
β_1	Number of eggs laid/ovipositing nulliparous female	60	(Delatte et al., 2009)
β_2	Number of eggs laid/ovipositing parous female	80	(Delatte et al., 2009)
σ	Sex-ratio at emergence	0.5	(Delatte et al., 2009)
μ_E	Minimum egg mortality rate (day^{-1})	0.05	(Tran et al., 2013)
μ_{em}	Mortality rate during emergence (day^{-1})	0.1	(Tran et al., 2013)
μ_{Fr}	Mortality rate related to seeking behaviour (day^{-1})	0.06	(Optimization)
μ_M	Mortality rate of males (day^{-1})	0.0735	(Oliva et al., 2013)
T_E	Minimal temperature needed for egg development (˚C)	10	(Delatte et al., 2009)
TDD_E	Total number of degree-day necessary for egg development (˚C)	110	(Tran et al., 2013)
γ_{Fem}	Development rate of emerging females (day^{-1})	0.4	(Tran et al., 2013)
γ_{Fo}	Transition rate from ovipositing to host-seeking females (day^{-1})	0.2	(Tran et al., 2013)
γ_{Fh}	Transition rate from host-seeking to engorged females (day^{-1})	0.2	(Tran et al., 2013)
T_{Fg}	Minimal temperature needed for egg maturation in females (˚C)	10	(Delatte et al., 2009)
TDD_{Fg}	Total number of degree-day necessary for egg maturation (˚C)	77	(Delatte et al., 2009)
κ_{Lfix}	Standard rainfall-independent environment carrying capacity for larvae	Field observations	
κ_{Lvar}	Standard rainfall-dependent environment carrying capacity for larvae	Field observations	
κ_{Pfix}	Standard rainfall-independent environment carrying capacity for pupae	Field observations	
κ_{Pvar}	Standard rainfall-dependent environment carrying capacity for pupae	Field observations	
Functions	**Definition**	**Expression**	**Ref**
f_E	Transition function from egg to larva	$\begin{cases} \dfrac{T(t) - T_E}{TDD_E}, & \text{if } (t) > T_E. \\ 0, & \text{otherwise.} \end{cases}$	(Tran et al., 2013)
f_L	Transition function from larva to pupa	$-0.0007T^2 + 0.0392T - 0.3911$	(Tran et al., 2013)
f_P	Transition function from pupa to emerging adult	$0.0008T^2 - 0.0051T + 0.0319$	(Tran et al., 2013)
m_E	Egg mortality	$\mu_E + \begin{cases} 0.1, & \text{if } R < 80. \\ 0, & \text{otherwise.} \end{cases}$	(Dieng et al., 2012; Tran et al., 2013)
m_L	Larva mortality	$0.02 + 0.0007e^{(0.1838(T-10))} + \begin{cases} 0.5, & \text{if } R < 80. \\ 0, & \text{otherwise.} \end{cases}$	(Delatte et al., 2009; Dieng et al., 2012)
m_P	Pupa mortality	$0.02 + 0.0003e^{(0.2228(T-10))} + \begin{cases} 0.5, & \text{if } R < 80. \\ 0, & \text{otherwise.} \end{cases}$	(Delatte et al., 2009; Dieng et al., 2012)
m_f	Female mortality	$0.025 + 0.0003e^{(0.1745(T-10))}$	(Delatte et al., 2009)
f_{Fg}	Transition function from engorged to oviposition site-seeking female	$\begin{cases} \dfrac{T(t) - T_{Fg}}{TDD_{Fg}}, & \text{if } (t) > T_{Fg}. \\ 0, & \text{otherwise.} \end{cases}$	(Tran et al., 2013)
f_{Fo}	Transition function from ovipositing to host-seeking female	$\gamma_{Fo}(1 + P_{norm})$	(Pachka et al., 2016)
f_F	Transition rate from nulliparous to parous females	$\dfrac{1}{1/f_{Fo} + 1/\gamma_{Fh} + 1/f_{Fg}}$	
K_L	Environment carrying capacity for larvae	$K_L(t) = \kappa_{Lfix} + \kappa_{Lvar} R_{norm}(t)$	(Tran et al., 2013)
K_P	Environment carrying capacity for pupae	$K_P(t) = \kappa_{Pfix} + \kappa_{Pvar} R_{norm}(t)$	(Tran et al., 2013)

Table 2

mALBORUN-SIT and mALBORUN-BSIT parameter values.

Parameters	Definition	Value and bounds	Ref
c	Sterile males competitiveness	0.23 [0.01 − 0.9]	(Bellini et al., 2007; 2013; Madakacherry et al., 2014; Oliva et al., 2012)
μ_{Ms}[a], μ_{Msc}[b]	Mortality rate of sterile males (day^{-1})	0.087 [0.18 − 0.065]	(Balestrino et al., 2010; Oliva et al., 2013)
k_F	Expected number of contaminating mating	1 [1 − 8]	Current work
k_B	Expected number of breeding sites that a female contaminates	1 [1 − 8]	Current work
d	Expected decontamination rate at breeding sites (day^{-1})	0.048 [0.08 − 0.0065]	(Caputo et al., 2012; Darriet and Corbel, 2006; Devine et al., 2009; Sihuincha et al., 2005; Snetselaar et al., 2014; Suman et al., 2014)
ϕ	Proportion of pupae surviving to pyriproxyfen	0.3 [0.02, 0.5]	(Caputo et al., 2012; Chang Moh et al., 2008; Darriet and Corbel, 2006; Devine et al., 2009; Snetselaar et al., 2014)
λ_{Ms}[a], λ_{Msc}[b]	Number of sterile males released /ha	1000 [600 − 6000]	(Bellini et al., 2013; Carvalho et al., 2015; Harris et al., 2011; Romeo et al., 2020)
τ	Periodicity of the releases (day)	7 [5 − 10]	(Bellini et al., 2013; Romeo et al., 2020)
n	Number of releases	18 [13 − 20]	(Bellini et al., 2013; Romeo et al., 2020)
T_{Start}	Starting date of the control period	01 sept. [1 Jan. - 31 Dec.]	

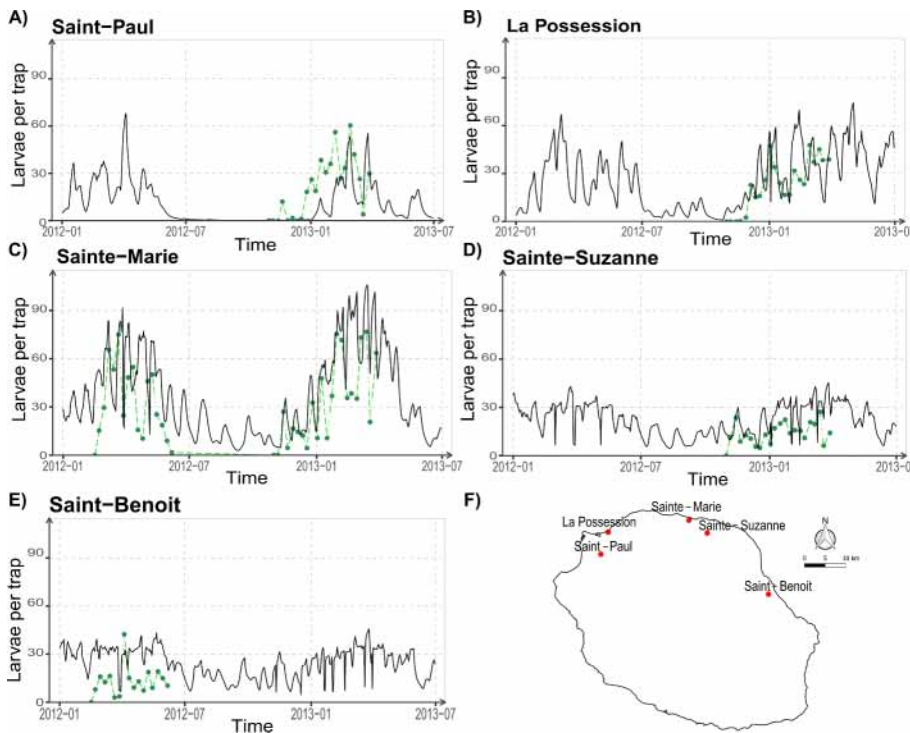[a] mALBORUN-SIT
[b] mALBORUN-BSIT

Fig. 6. mALBORUN model validation. *The simulated dynamics of larvae (black lines) was compared to field data (green points) collected in 2012 and 2013 at A) Saint-Paul, B) La Possession, C) Sainte-Marie, D) Sainte-Suzanne and E) Saint-Benoit sites. F) The sites are located in the North of La Reunion Island. Parameter values and functions of the model are in Table 1.*
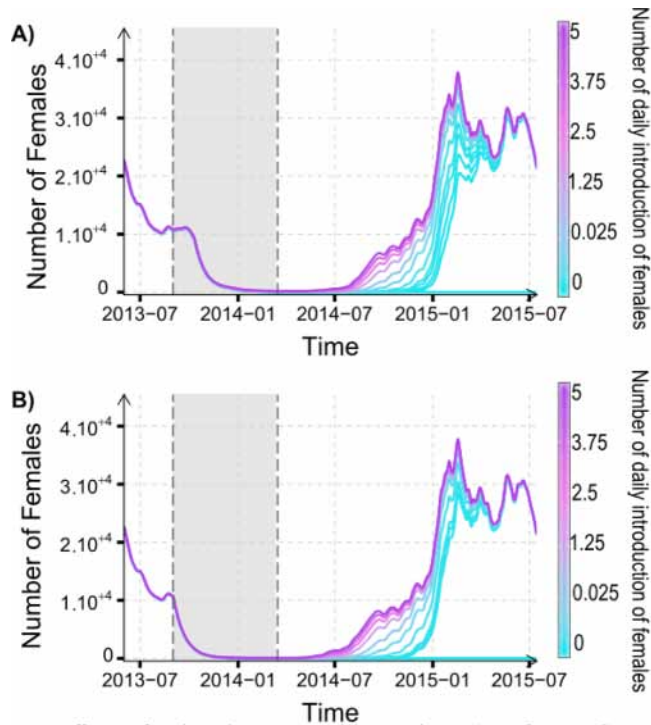

Fig. 7. Effect of migration on resilience in mALBORUN-SIT A) and mALBORUN-BSIT B). *From one female every 40 days (introduction = 1/40) to five females per day (introduction = 5) were allowed to enter the target population during and after sterile male release. Weather data at the Duparc Sector from La Reunion Island were used as example. Parameter values and functions of the models are in Tables 1 and 2.*

3.2. The number of sterile males released, their competitiveness and the timing of release are the key parameters of the control

To assess the most influential parameters, a SA was performed for the mALBORUN-SIT and mALBORUN-BSIT models. We analyzed four model outputs: the reduction rate, the sterility rate, the resilience time and the reduction of emergence (see Methods). Surprisingly, it was shown that the resilience time (*i.e* the time required after the treatment stopped for a treated population to reach a size similar to a untreated population) was not normally distributed. This was due to the complete elimination of the population that was predicted for some parameters sets: As the model was run on an isolated population, without migration, no resilience was possible. To verify whether these elimination events were maintained in the presence of a limited migration or rather a no-migration artifact, we simulated the introduction of adult females into the population, from one female every 40 days to five females per day. A total of 12 simulations were performed (Fig. 7). The results showed that even very low immigration was sufficient enough for the population to eventually return to its natural dynamics, in sharp contrast with the elimination predicted in the no-migration case: it thus suggested that the local eliminations were indeed artifacts. Consequently, we decided to perform another SA with the introduction of a few females (one every 40 days as shown in Fig. 7).

For both models, the reduction rate relative to the number of females ($F_n + F_p$) without control was not normally distributed and could therefore not be analyzed.

Considering mALBORUN-SIT model (Fig. 8A), the competitiveness of the sterile males (c) was identified as the most influential parameter for both sterility rate and resilience (> 50%). The number of sterile males released (λ_{M_s}) and the starting date of the control period (T_{Start}) were the second most influential parameters (*ca.* 25% each), for both outputs. Finally, a strong effect of the number of releases (n) was
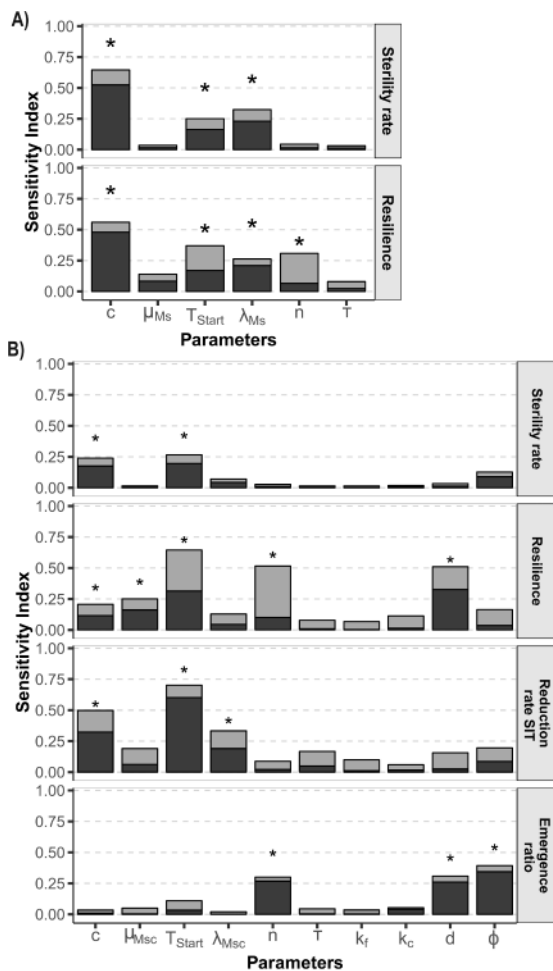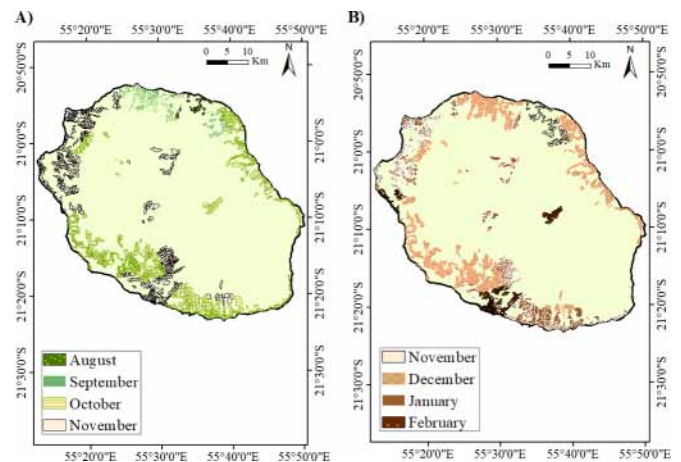
Fig. 9. Map of the optimal starting months for the sterile males releases at La Reunion Island. *The optimal date was estimated by optimizing the outputs for A) mALBORUN-SIT and B) mALBORUN-BSIT over three years. The optimal date is the same for all the sectors connected to the same weather station.*

ϕ). Finally, two of these specific parameters had, as expected, a strong influence on the emergence ratio: the proportion of pupae surviving pyriproxyfen ϕ and the expected duration of contamination at larval sites $\frac{1}{d}$.

For both models, the SA showed that there was a high impact of first-order parameter interactions on the outputs. For example, during the control period, an *Ae. albopictus* population reduction rate of 0.8 can be achieved either with $c = 0.6$ and $\lambda_{Ms} = 2800$ sterile males/ha, or with a competitiveness of $c = 0.4$ and $\lambda_{Ms} = 4000$ sterile males/ha with the SIT (Fig. 10A). Similarly for boosted SIT, $c = 0.6$ and $\lambda_{Msc} = 1200$, or $c = 0.4$ and $\lambda_{Msc} = 1800$, achieve the same population reduction of 0.8; note that fewer males need to be released compared to SIT (Fig. 10B).

3.3. Boosted SIT control should start later than SIT

As shown by the SA, the starting date of the release of sterile males (T_{Start}) was a key parameter for both SIT and boosted SIT. A map was produced for each control method that shows the specific optimal T_{Start} for each operational urban sectors (that depends on local climatic conditions). For SIT (Fig. 9A and Fig. B1), the date to begin the release was optimal when the density of *Ae. albopictus* population was low, thus on average, in October, at the end of the austral winter (May - October). For boosted SIT (Fig. 9B and Fig. C1), the optimal date was postponed by several months, on average in December, when the population density of *Ae. albopictus* has already increased Fig. C1.

3.4. Boosted SIT carries higher benefits when sterile males are poor competitors

The other important parameters identified by the SA were competitiveness (c) and the number of sterile males released (mALBORUN-SIT: λ_{Ms}, mALBORUN-BSIT: λ_{Msc}). However these two parameters are in direct interaction: The more competitive the sterile males are, the fewer released males are needed to obtain similar results in terms of relative reduction rate or resilience. Although we plotted the impact of paramter c alone on *Ae. albopictus* population control with SIT and
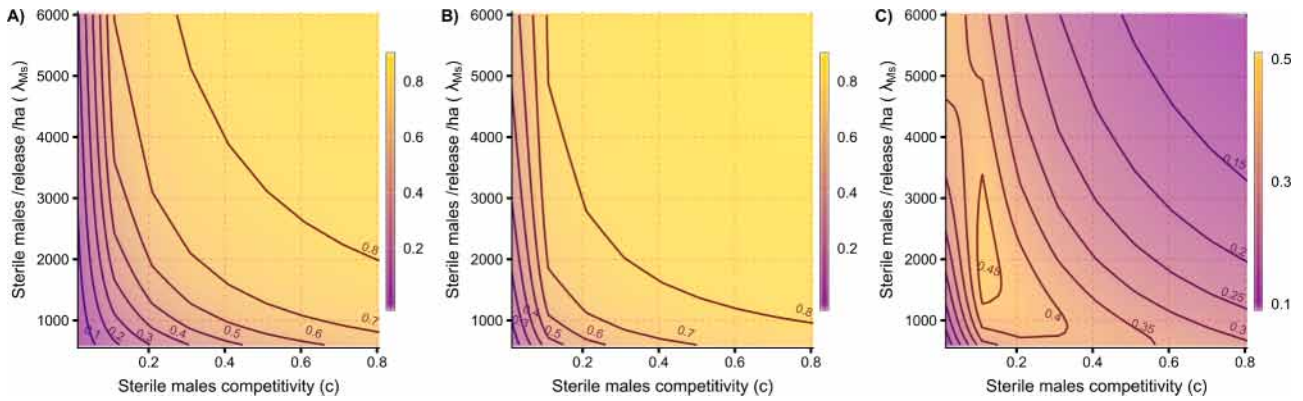

Fig. 8. Sensitivity indices of the Fourier amplitude sensitivity test (FAST) for mALBORUN-SIT A) and mALBORUN-BSIT B) outputs. *In dark grey, main effects; in light grey, interactions. 256,000 simulations with 6400 points per parameter and four replicates. Parameters contributing to more than 20% of the output variance were considered to be influential parameters (identified by a star for each output). See Table 2 for parameter definitions. To prevent the eradication artifacts due to the absence of migration (see 3.2), one female was introduced every 40 days in each operational urban sector. Parameter values and functions of the models are in Tables 1 and 2.*

detected on resilience, mainly through interactive effects.

For the mALBORUN-BSIT model (Fig. 8B), the results of the SA were slightly different: while both the starting date of the control period (T_{Start}) and the competitiveness of the sterile males (c) were the determinants of the sterility rate and remained influential on resilience, c appeared less determinant than in mALBORUN-SIT (*ca.* 25%). Similarly, the number of sterile males released (λ_{Ms}) no longer had any influence. However, the number of releases (n) remained influential on resilience, as well as two additional parameter, the mortality rate of sterile males ($\mu_{M_{sc}}$) and the expected duration of contamination at larval sites (d).

We also assessed the main parameters influencing the observed differences in reduction rates between SIT and boosted SIT applications. They were again explained mainly by T_{Start}, c and λ_{Msc}, rather (which is surprising) than by parameters specific to mALBORUN-BSIT (k_F, k_B, d,

Fig. 10. Impact of the number of sterile males released and of their competitiveness on the female numbers ($F_n + F_p$) reduction. *The reduction of the abundance of adult females is indicated A) for SIT (mALBORUN-SIT) relatively to a non-controlled population (mALBORUN); B) for boosted SIT (mALBORUN-BSIT) relatively to a non-controlled population (mALBORUN); and C) for boosted SIT (mALBORUN-BSIT) relatively to a population controlled with SIT (mALBORUN-SIT). The reduction proportion is represented by a color gradient from purple (low reduction) to yellow (large reduction), with isoclines represented with a contour plot (from 0.1 to 0.8 reduction). The weather conditions of a single sector were used for the simulations (i.e. Duparc Sector at La Reunion Island). To prevent the eradication artifacts due to the absence of migration (see text), one female was introduced every 40 days in each the operational urban sectors.*
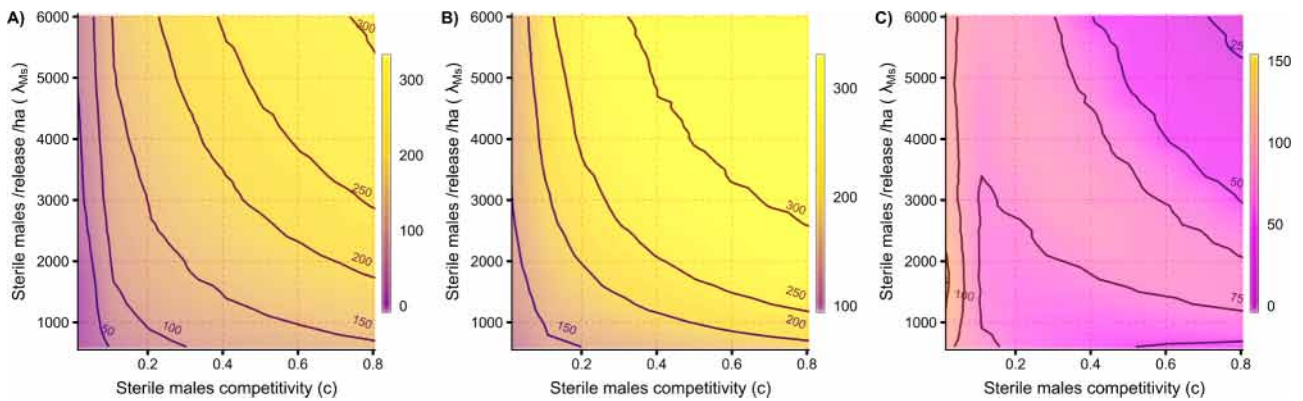

Fig. 11. Impact of the number of sterile males released and of their competitiveness on the population resilience time. *The time required for a treated population to reach the population size it would have had without treatment (mALBORUN) is indicated A) for SIT (mALBORUN-SIT) ; B) for boosted SIT (mALBORUN-BSIT). The resilience time difference between the two control methods is indicated in C). The resilience time is represented by a color gradient from purple (fast resilience) to yellow (slow resilience), with isoclines represented with a contour plot (every 50 days required for resilience). The weather conditions of a single sector (Duparc Sector at La Reunion Island) were used for the simulations. To prevent the eradication artifacts due to the absence of migration (see text), one female was introduced every 40 days in each the operational urban sectors.*

boosted SIT, (Fig. F1 and Fig. F2), it is more relevant to analyse the combined effect of c and $\lambda_{M_{Sc}}/\lambda_{M_S}$.

We first analyzed how this interaction impacts the reduction rate in female numbers ($F_n + F_p$), for each control method independently (Fig. 10A: SIT, Fig. 10B: Boosted SIT). For both methods, the reduction rate increased with c, λ_{M_S} and $\lambda_{M_{Sc}}$, but the competitiveness was clearly the main determinant. In order to assess the added benefits of the boosted SIT method, we also calculated the difference in the reduction rate between mALBORUN-SIT and mALBORUN-BSIT for various combinations (Fig. 10C): It appeared that the boosted SIT was mostly beneficial when the sterile males were poor competitors, but not too poor ($0.17 < c < 0.4$).

We then analyzed how the interaction between the number of sterile males released and their competitiveness impacted the resilience time, for each control method independently (Fig. 11A: SIT, Fig. 11B: Boosted

SIT). As for reduction rate, and for both methods, the resilience time increased with c, λ_{M_S} and $\lambda_{M_{Sc}}$, but the competitiveness was again clearly the main determinant. In order to assess the added benefits of the boosted SIT method, we also calculated the difference in resilience time between mALBORUN-SIT and mALBORUN-BSIT for various combinations (Fig. 11C): It appeared that boosted SIT was again mostly beneficial when sterile males were poor competitors.

3.5. Constant releases are better than density-dependent releases

We compared the impact on reduction rates and resilience times for two control strategies differing in the number of sterile males released (mALBORUN-SIT: λ_{M_S}, mALBORUN-BSIT: $\lambda_{M_{Sc}}$): i) A constant number during the control period and ii) a number proportional to the number of adult females at the time of release. The second release strategy has

been proposed to reduce the rearing cost of the sterile males.

For both models, the first strategy appeared more efficient: the population was reduced to a greater extent and returned to its initial dynamics more slowly after the control period (Fig. D1). However, while the difference between the two release strategies was relatively small in terms of reduction rates, the resilience time was much more affected, since it was reduced by about 3 times with the second strategy. For example for SIT, with $n = 7$ days and $\lambda_{M_s} = 10$ times the number of females, the population was reduced by 95% and required 335 days to return to natural dynamics with constant releases, while for proportional releases the population was decreased by 82% and only needed 92 days to return to natural dynamics. Similar results were obtained for boosted SIT (Fig. E1).

4. Discussion

We developed a weather-driven abundance model of *Ae. albopictus* at La Reunion island (mALBORUN) based on the ALBORUN mechanistic model Tran et al. (2020), and integrated the effects of SIT (mALBORUN-SIT) and boosted SIT (mALBORUN-BSIT) on population dynamics. These non-autonomous models include the impact of temperature and rainfall, which are two important drivers of the mosquito dynamics (Agusto et al., 2015; Delatte et al., 2009; Dieng et al., 2012; Kruijf et al., 1973; Roiz et al., 2010; Tran et al., 2020). The predicted abundance of mosquito populations follows environmental fluctuations (Fig. 5) and was consistent with entomological field collections (Fig. 6). Thus, our models are adapted to areas with a high climatic spatial heterogeneity, as it is the case in La Reunion island. To our knowledge, these are the first models that integrate real weather data in order to analyze the effects of SIT and boosted SIT on mosquito populations. Non-autonomous models were chosen because, as White et al. (2010) pointed out, environmental data are of major importance to optimize these control strategies, particularly to determine the optimal period for effective releases of sterile males (Fig. H1). Our results have indeed shown that the multitude of microclimates in La Reunion island lead to different optimal starting months depending on the areas concerned by the release of sterile males (Fig. 9).

4.1. Migration should be considered in future models

According to our results, both SIT and boosted SIT could lead to virtual elimination of *Ae. albopictus* populations: in both models, as the populations are modeled independently, some sets of parameters induced a density equilibrium close to zero after treatment (Fig. 7). Nevertheless, we have shown that this result is probably an artifact due to the non inclusion of mosquito dispersal in the models. Although Lacroix et al. (2009) has shown a relatively low dispersal ability for *Ae. albopictus*, simulations showed that the introduction of even a tiny number of females would result in a rapid recovery of the mosquito population after the treatments (Fig. 7). It is still possible that some Allee effect (not modelled here) may be induced by the reduction in the number of successful mating when males densities become low (this would increase the difficulty of finding a mate), which would delay the population's regrowth and increase the probability of sustainable elimination after treatment (Li et al., 2007; Li and Yuan, 2015; Strugarek et al., 2019). Nevertheless, our results are consistent with a recent pilot trial of transgenic *Ae. aegypti* males releases in Brazil, which showed that the population had not been eliminated despite a significant decrease in wild mosquito populations during the control period (Garziera et al., 2017). The future integration of adult mosquito

migration into our model, taking into account the heterogeneity of environment and its impact on migration rates, would therefore be a crucial development to provide more accurate quantitative predictions (Dunning et al., 1995).

4.2. Competitiveness vs. number of released males equilibrium, and control timing are crucial for SIT efficiency

According to the SA results for the mALBORUN-SIT model, the competitiveness and the quantity of sterile males released are the two most important parameters that determine the effective control of *Ae. albopictus* populations (Fig. 8A). Similarly to previous findings by Pleydell and Bouyer (2019), appropriate combinations of these two parameters values could indeed lead to important population reductions (Fig. 10). However, other studies have shown that this competitiveness is highly variable depending on local conditions at the sterile-males release sites (e.g. Bellini et al., 2007; Bellini et al., 2013; Madakacherry et al., 2014; Oliva et al., 2012). Thus, an accurate estimate of this competitiveness, in the environment where releases occur, is necessary to improve the predictive capacity of the model and to assess the efficiency of this strategy in a particular field context. As underlined by White et al. (2010), reduced competitiveness of sterile males can be offset by larger releases (Fig. 8), and our model allows an accurate estimate of this balance. It should be noted that increasing the number of released males would entail additional, and potentially high, economic costs.

The starting month for the sterile males releases is also a crucial parameter for the SIT control method (Fig. 9). According to our results, the best date corresponds to the end of the austral winter, when the wild mosquito populations are at the lowest density: As there are fewer wild competitors, sterile males have a higher probability of mating with females (Dufourd and Dumont, 2012; Huang et al., 2017; White et al., 2010), which may partly compensate their lower competitiveness. However, and despite the additional cost, we have shown here that the full benefit of these early releases requires a significant and consistent number of sterile males from the start (Fig. D1), rather than a number of males released proportionally to the number of wild adult females (Cai et al., 2014; Li and Yuan, 2015). Again our model allows for accurate forecasts under various scenarios, and can therefore help control agencies in making informed operational decisions.

4.3. Boosted SIT could be an interesting improvement, but some parameters need to be evaluated before implementation

The mALBORUN-BSIT model analyses showed that coating sterile males with pyriproxyfen could potentially improve the efficiency of the SIT control. The additional population reduction due to this "boost" is particularly strong (up to 45% more than SIT alone) for sterile males with intermediate competitiveness (*i.e.* $0.2 < c < 0.5$, Fig. 10C); it cannot compensate too poor males ($c < 0.2$), and provide lower improvements when they are already good competitors ($c > 0.5$). Similarly, boosted SIT could significantly increase the population resilience time, up to 75 more days again for males with intermediate competitiveness and for reasonable number released (Fig. 11C). This strategy would thus be most interesting in contexts where increasing the quality of the males released is difficult, due to the direct effects of the sterilizing radiations and/or the effects of mass-rearing in production facilities. However, an estimation of the relative costs of the coating boost or of producing more males should be considered too, and our model provides a reliable framework for such analyzes.

As for SIT alone, the timing of boosted SIT implementation appears crucial: the boost effects are more visible in early austral summer (Fig. 9). This confirms the work of Pleydell and Bouyer (2019) who have shown that the boosted-SIT must be applied when the population begins to increase: when the population is too low, only a small amount of pyriproxyfen is transferred to females and therefore to breeding sites, so that the boosting effect is lost. It should be noted that, in choosing conservative hypotheses for our study, we did not consider direct contamination of breeding sites by males. Yet, this contamination may occur as some *Ae. aegypti* males were found in sticky ovitraps (Ritchie et al., 2003). Direct contact of contaminated males with breeding sites could slightly increase the effectiveness of the pyriproxyfen transfer from females under these conditions (Mains et al., 2015). However, the obvious advantage of the boosted approach is that the starting date of releases is delayed: consequently, fewer releases are needed for a similar effect.

Two other parameters appeared to be significant (although much less important than the previous ones) in the success of the boosted SIT control method: the duration of pyriproxyfen contamination of breeding sites, confirming (Pleydell and Bouyer, 2019), and the proportion of pupae surviving pyriproxyfen, both related to the dose of the contaminants. Crucially, the relative importance of these two parameters actually highlights the limitations of our predictions: although qualitatively robust, our results should be taken with caution for quantitative predictions. For several key parameters of the model, there is indeed little or no empirical data, mainly because the concept of boosted SIT is recent. Several studies are currently in progress to improve the coating technique. Similarly, the efficiency of the male/female and female/breeding sites contamination remains to be determined experimentally, both in the laboratory and under natural conditions. Finally, we did not consider the potential direct impacts of pyriproxyfen on female fecundity and/or on the hatching rate, which could modify the boosting effect: some have been described, but they appear to vary depending on the formulation of pyriproxyfen used (Dell Chism and Apperson, 2003; Itoh et al., 1994; Mbare et al., 2013; Unlu et al., 2017). Again, additional experimental studies are needed to adjust the BSIT model to more realistic conditions and provide quantitatively accurate predictions.

4.4. SIT and boosted SIT should be part of integrated management strategies against *Aedes albopictus*

Our study clearly shows that for realistic sets of key parameters, SIT could provide effective control of mosquito populations, and that boosted SIT could even improve this efficiency. Compared to the classical use of chemical insecticides, boosted SIT based on pyriproxyfen would be used in a very targeted way, at very low doses. Moreover, the contaminated mosquitoes are expected to specifically contaminate their small and mostly artificial breeding sites, created and maintained by humans, which should limit any risk of environmental contamination. However, as with any use of chemical insecticides, the autodissemination of pyriproxyfen to boost the SIT can lead to the development of mosquito resistance (Tantely et al., 2010; Vontas et al., 2012; Zaim and Guillet, 2002). mALBORUN-BSIT model provides a solid framework for studying the potential evolution of insecticide resistance in mosquito populations in order to prevent its occurrence or control its spread by optimizing the use of the boosted SIT under various scenarios (Barbosa et al., 2018). Moreover, if the coating with the pyriproxyfen is more advanced, other candidates have been proposed, like the use of natural biocides such as densovirus (Carlson et al., 2006). Again, our

model provides the appropriate framework for evaluating this method *in silico*.

SIT and boosted-SIT are not the only alternative control methods available in the literature or in the field: they are and should be considered as alternative tools in a broader set, with complementary actions. Mass trapping of adult mosquitoes, for example, have shown promising results (Barrera et al., 2017; Degener et al., 2014). While our study focused on sterile males release techniques, Pleydell and Bouyer (2019) studied, for example, the effects of SIT and boosted SIT coupled with the disposition in the environment of artificial oviposition sites contaminated with pyriproxyfen (autodissemination station). Interactions between different method controls used simultaneously or sequentially could be positive or negative (Barclay, 1987; Knipling, 1979) and should be considered to optimize mosquito population control. Our mechanistic model that takes into account the different stages of the mosquito life cycle provides an appropriate framework for implementing and testing alternative mosquito control methods compared to, or in combination with, SIT and boosted SIT, and would be a valuable tool to guide vector control policies. It could also be coupled with an epidemic model to study the impact of control methods on the basic reproduction rate (R0) of diseases (e.g. Danbaba and Garba, 2018a; Danbaba and Garba, 2018b; Dumont and Chiroleu, 2010; Hendron and Bonsall, 2016; Mishra et al., 2018).

5. Conclusion

The control of *Ae albopictus* based on sterile males release techniques in La Reunion Island was modelled for the first time with a weather-driven model validated by entomological field data. The results show that sustainable control of *Ae albopictus* populations is possible with SIT, but depends strongly on an equilibrium between the relative competitiveness of the sterile males compared to wild ones and the number of males released, as well as on the starting month of the control. It also showed that even low migration can affect population dynamics and should be taken into account, and that it is preferable to carry out pulsed releases with a constant number of males released during the control period. Our study also showed promising results for boosted SIT: it can significantly improve the efficiency of SIT when the sterile males released have a moderate competitiveness, and allows for later (and shorter) control implementation. Our model provides a solid framework for the future development of operational tools to enable control agencies to make informed decisions, particularly for the implementation of integrated management strategies to control arbovirus transmission.

CRediT authorship contribution statement

Marion Haramboure: Methodology, Software, Formal analysis, Writing - original draft, Visualization. **Pierrick Labbé:** Methodology, Validation, Formal analysis, Writing - review & editing, Supervision. **Thierry Baldet:** Validation, Writing - review & editing, Project administration. **David Damiens:** Writing - review & editing, Data curation. **Louis Clément Gouagna:** Writing - review & editing, Data curation. **Jérémy Bouyer:** Conceptualization, Resources, Writing - review & editing, Project administration, Funding acquisition, Data curation. **Annelise Tran:** Methodology, Validation, Formal analysis, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgements

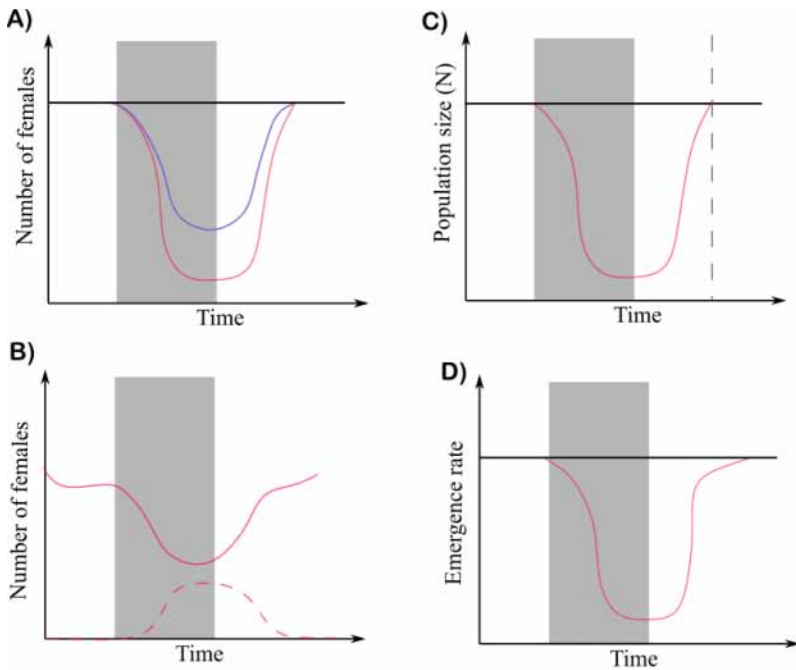## Appendix A. Model outputs

Fig. A1. Schematic representation of the models' outputs. *The reduction rate A), the sterility rate B), and the time to return to the natural dynamics C) are the outputs for mALBORUN-SIT and mALBORUN-BSIT models. The reduction of emergence D) is mALBORUN-BSIT output only. The gray square corresponds to the period of control. The black line corresponds to the outputs of the reference mALBORUN model, the blue and red lines correspond to the outputs of mALBORUN-SIT and mALBORUN-BSIT, respectively. In the Figure B), the continuous line corresponds to the total number of fecundated females ($F_n + F_p + F_s$), while the dotted line corresponds to the number of sterile females f_s. In Figure C), the vertical black dotted line corresponds to the time needed to return to the natural dynamics after treatment (resilience). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)*

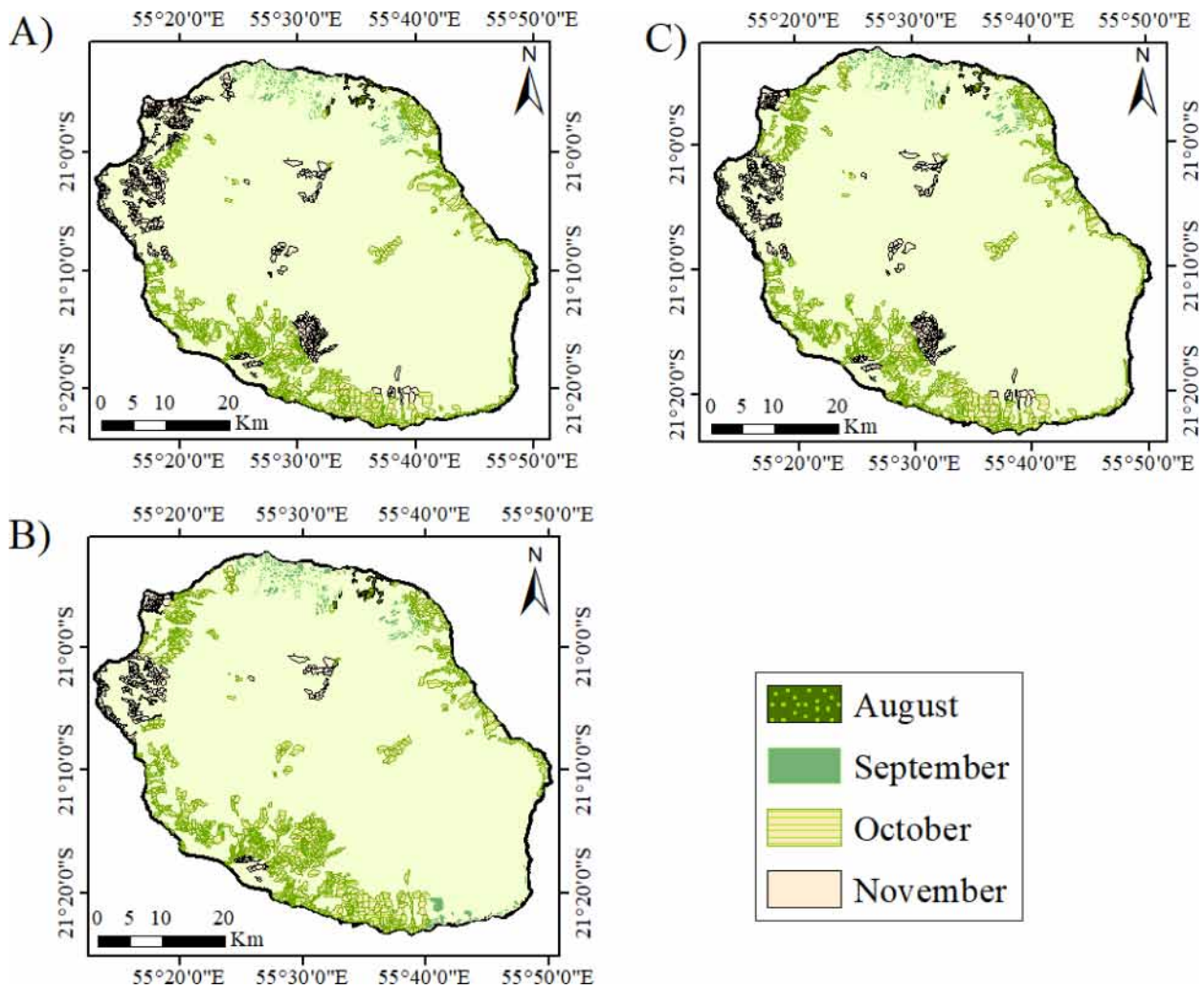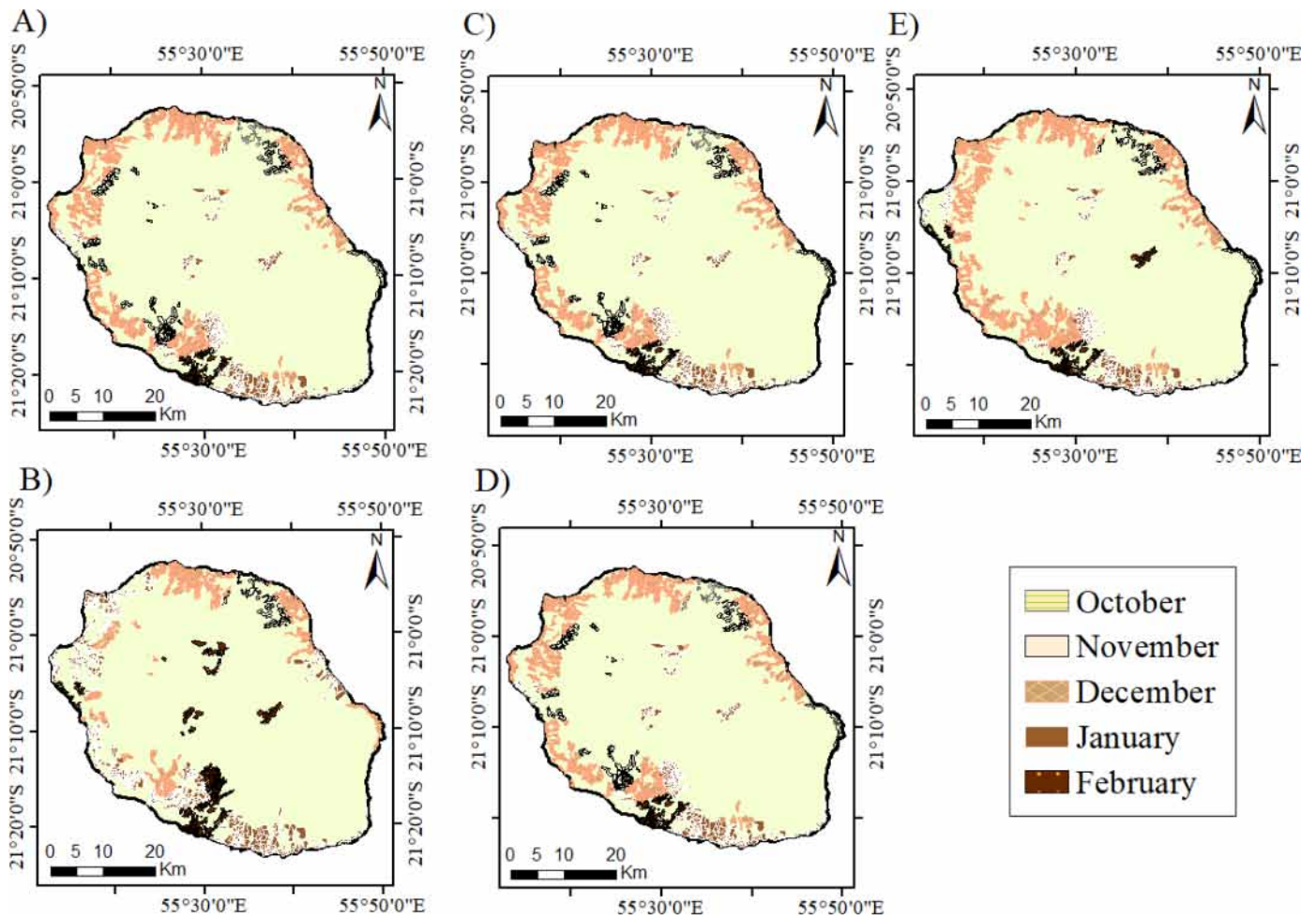**Appendix B. Map of the optimal starting month for SIT**

Fig. B1. Optimal starting month for the outputs of the mALBORUN-SIT model at La Reunion Island. *Map of the optimal release starting month for the reduction rate A), the sterility rate B), and the time to return to the natural dynamics C) are the outputs for mALBORUN-SIT model over three years. The optimal month is the same for all the sectors connected to the same weather station.*

Appendix C. Map of the optimal starting month for boosted SIT

Fig. C1. Optimal starting month for the outputs of the mALBORUN-BSIT model at La Reunion Island. *Map of the optimal release starting month for the reduction rate between boosted SIT application and non-controlled population A) or SIT-controlled population B), the sterility rate C), the time to return to the natural dynamics D) and E) are the outputs for mALBORUN-BSIT model over three years. The optimal month is the same for all the sectors connected to the same weather station.*.

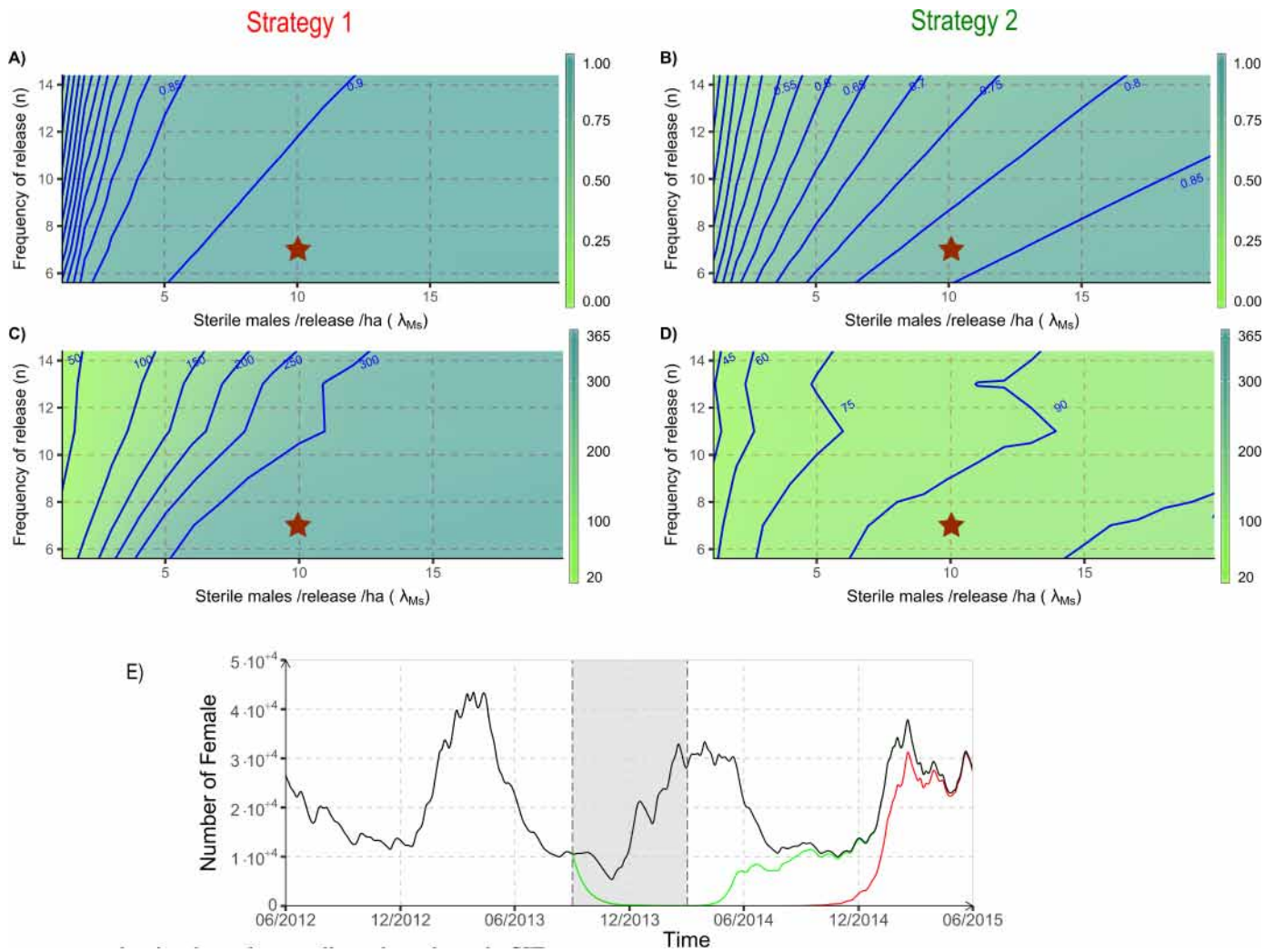**Appendix D. Number of sterile males released for SIT**

Fig. D1. Constant *versus* density-dependent sterile males release in SIT *The impacts of two release strategies for the number of sterile males, constant (strategy 1) and proportional to the adult females density (strategy 2) are presented (on the left and right, respectively). The proportional reduction of the population size compared to a non-treated population (mALBORUN-SIT vs. mALBORUN) is represented with a contour plot (ranging from 0.55% to 0.9) for A) constant releases and B) proportional releases. The resilience time is represented with a contour plot (ranging from 45 to 300 days) for C) constant releases and D) proportional releases. Ten values of λ_{M_s} were tested, from 1, to 10 times the number of adult females at the beginning of the control period (strategy 1) or during the release dates (strategy 2). Six τ were tested, from 15 days down to 5 days. (E) Population dynamics without control (in black), with constant releases (in red) and with proportional release (in green), for $\tau = 7$ days and $\lambda_{M_s} = 10$ (star on panels A, B, C and D); the control period is grayed. The weather conditions of a single sector were used for the simulations (i.e. Duparc sector at La Reunion Island). To prevent the eradication artifacts due to the absence of migration (see text), one female was introduced every 40 days in each the operational urban sectors. Parameter values and functions of the model are in Tables 1 and 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)*

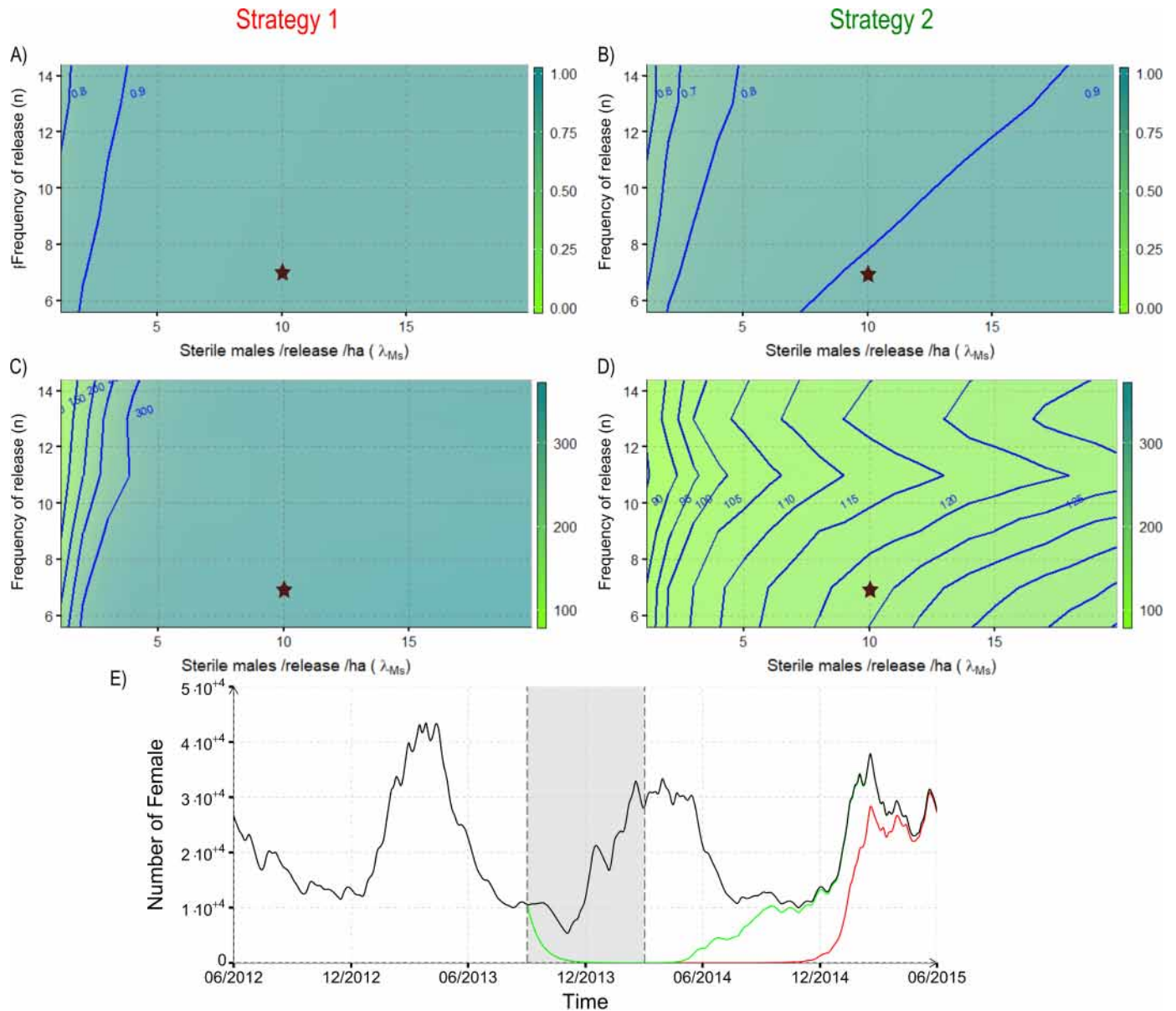**Appendix E. Number of sterile males released for boosted SIT**

Fig. E1. Constant *versus* density-dependent sterile males release in the boosted SIT *The impacts of two release strategies for the number of sterile males, constant (strategy 1) and proportional to the adult females density (strategy 2) are presented (on the left and right, respectively). The proportion reduction of the population size compared to a non-treated population is represented with a contour plot (ranging from 0.6% to 0.9) for A) constant releases and B) proportional releases. The resilience time is represented with a contour plot (ranging from 90 to 300 days) for C) constant releases and D) proportional releases. Ten values of λ_{M_s} were tested, from 1, to 10 times the number of adult females at the beginning of the control period (constant releases) or during the release dates (proportional releases). Six τ were tested, from 15 days down to 5 days. (E) Population dynamics without control (in black), with strategy 1 (in red) and with strategy 2 (in green), for $\tau = 7$ days and $\lambda_{M_s} = 10$ (star on panels A, B, C and D); the control period is grayed. The weather conditions of a single sector were used for the simulations (i.e. Duparc sector at La Reunion Island). To prevent the eradication artifacts due to the absence of migration (see text), one female was introduced every 40 days in each the operational urban sectors. Parameter values and functions of the model are in* Tables 1 *and* 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Appendix F. Impacts of variations in sterile male competitiveness (*c*)

The reduction and sterility rates of the population increases sharply with increasing competitiveness (*c*) of the sterile males (M_s or M_{sc}, for SIT or BSIT, resp.), until it reaches a plateau. While emerging females sterilization was modeled identically, a higher sterility rate was observed with boosted SIT than with SIT. This difference is due to the fact that the greater population reduction induced by boosted SIT increases the probability of sterile males to encounter emerging females and sterilize them. In terms of population resilience after the control period, no difference was observed for the selected parameter set. Similarly, competitiveness (*c*) did not have much impact on pupal emergence for boosted SIT.
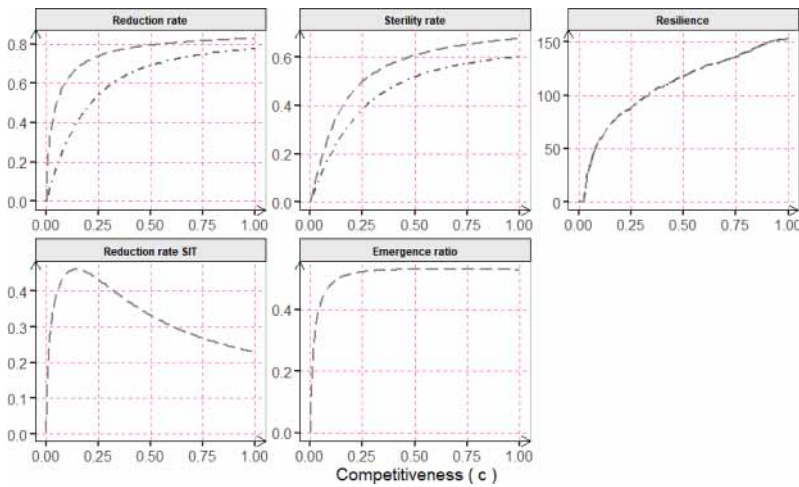

Fig. F1. Impact of the competitiveness parameter (*c*) variation on mALBORUN-SIT and mALBORUN-BSIT model outputs *The dynamics of a population controlled with SIT (mALBORUN-SIT) and boosted SIT (mALBORUN-BSIT) are represented with dashed line and dotted line, respectively. Parameter values and functions of the models are in Tables 1 and 2.*
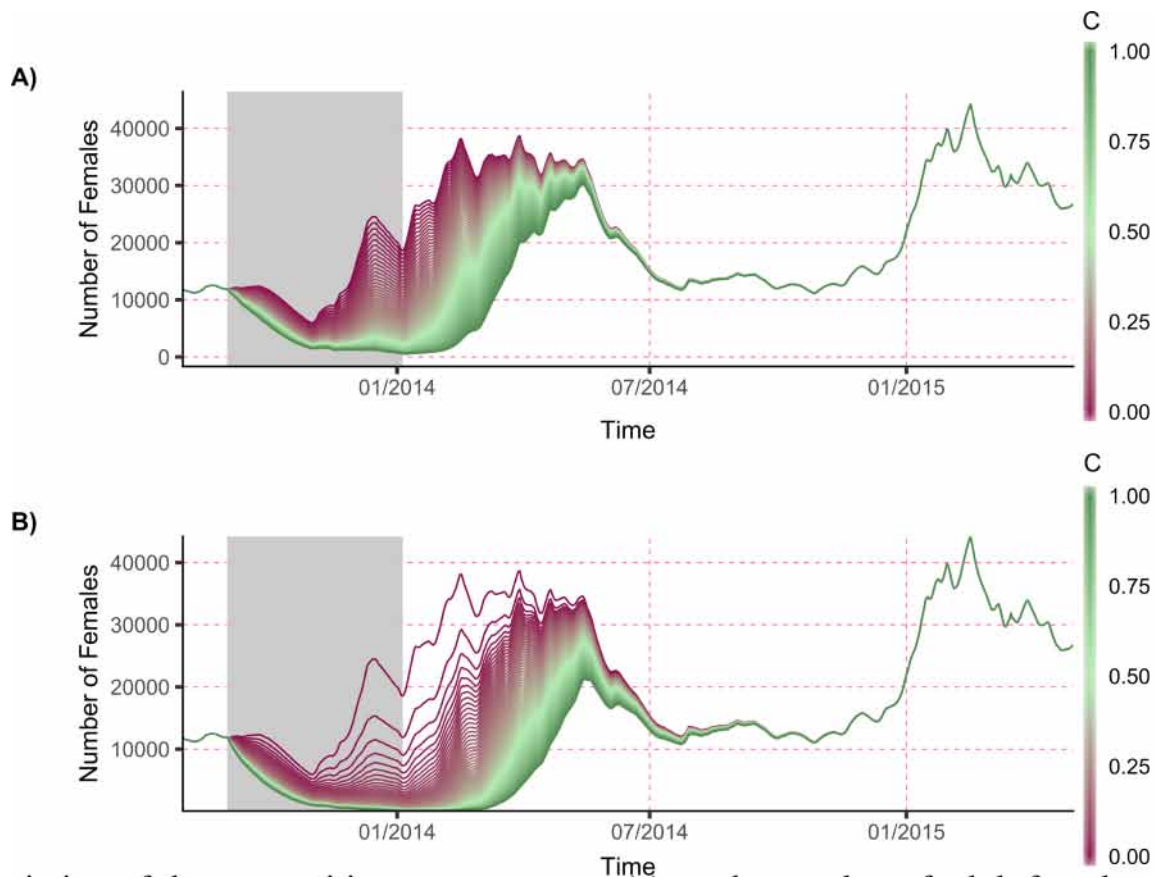

Fig. F2. Impact of the variation of the competitiveness parameter (*c*) on the number of adult females (nulliparous (F_n) + parous (F_p)) *Competitiveness (c) increases from purple (c = 0: low competitiveness) to yellow (c = 1: high competitiveness). The grey background indicates the control period. Weather inputs were those of the Duparc Sector, Reunion Island. Parameter values and functions of the models are in Tables 1 and 2.* (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

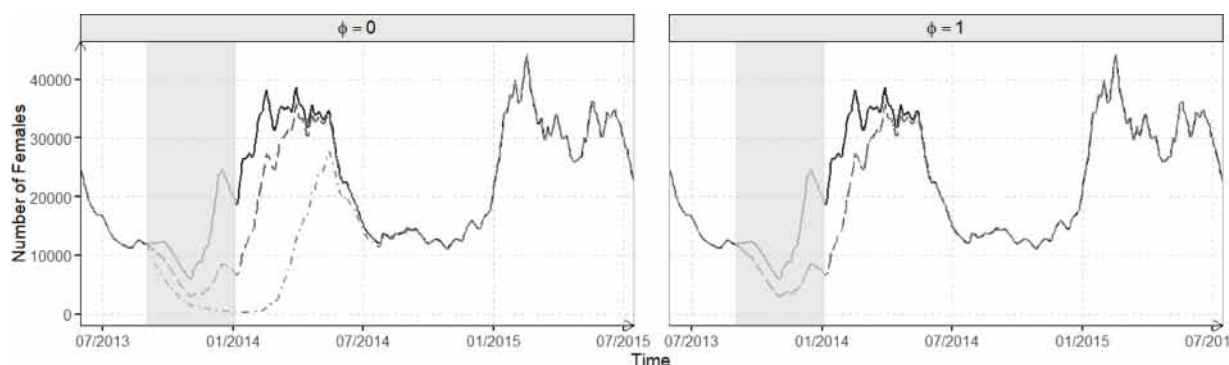## Appendix G. Variation of the proportion of pupae surviving to pyriproxyfen (ϕ) in the mALBORUN-BSIT model

Fig. G1. Impact of the proportion of pupae surviving exposure to pyriproxyfen ϕ on the number of adult females (nulliparous (F_n) + parous (F_p)) *Population dynamics without control (mALBORUN) is represented in solid line and the population dynamics controlled with SIT (mALBORUN-SIT) and boosted SIT (mALBORUN-BSIT) are represented in long dashed line and in dotted line respectively. When $\phi = 0$ (left), no emergence is possible so that the boosted SIT effect is maximum, for both population reduction and resilience; when $\phi = 1$ (right) all the pupae can emerge (e.g. resistance of Ae. albopictus to pyriproxyfen) so that the boosting effect is null. The grey background indicates the control period. Weather inputs were those of the Duparc sector, Reunion Island. Parameter values and functions of the models are in Tables 1 and 2.*

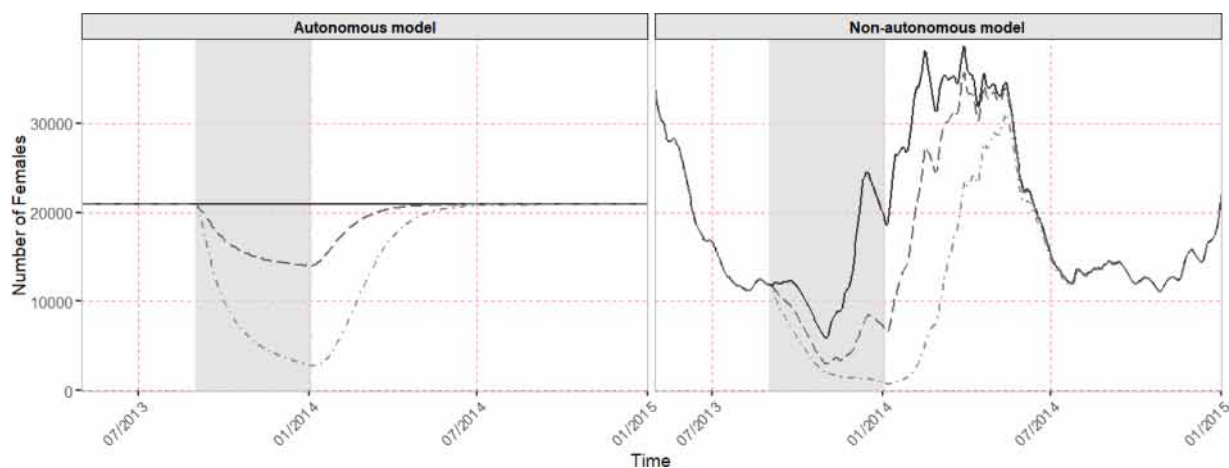## Appendix H. Autonomous and non-autonomous models

Fig. H1. Number of adult females (nulliparous (F_n) + parous (F_p)) in autonomous and non-autonomous models *Temperature and precipitation of the autonomous model were set at the average value of temperatures and precipitation recorded in the Duparc sector from 2011 to 2016. Population dynamics without control (mALBORUN) is represented in solid line and the population dynamics controlled with SIT (mALBORUN-SIT) and boosted SIT (mALBORUN-BSIT) are represented in long dashed line and in dotted line respectively. The grey background indicates the control period. Weather inputs were those of the Duparc sector, Reunion Island. Parameter values and functions of the models are in Tables 1 and 2.*

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