Imported chikungunya cases in an area newly colonised by Aedes albopictus : mathematical assessment of the best public health strategy

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Research article

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We aimed to identify the optimal strategy that should be used by public health authorities against transmission of chikungunya virus in mainland France. The theoretical model we developed, which mimics the current surveillance system, predicted that without vector control (VC), the probability of local transmission after introduction of viraemic patients was around 2%, and the number of autochthonous cases between five and 15 persons per hectare, depending on the number of imported cases. Compared with this baseline, we considered different strategies (VC after clinical suspicion of a case or after laboratory confirmation, for imported or autochthonous cases): Awaiting laboratory confirmation for suspected imported cases to implement VC had no significant impact on the epidemiological outcomes analysed, mainly because of the delay before entering into the surveillance system. However, waiting for laboratory confirmation of autochthonous cases before implementing VC resulted in more frequent outbreaks. After analysing the economic cost of such strategies, our study suggested implementing VC immediately after the notification of a suspected autochthonous case as the most efficient strategy in settings where local transmission has been proven. Nevertheless, we identified that decreasing reporting time for imported cases should remain a priority.

Introduction

Environmental changes are a significant cause for concern for public health authorities [1,2]. Global warming [3], decline in biodiversity [4], urbanisation [5] or globalisation [6] can facilitate the spread of vectors and increase pathogen transmission. While some of these changes occur over the course of several years or decades and could therefore represent a problem in the long term, invasive vector species that can transmit pathogens such as dengue or chikungunya viruses expose new human populations to new pathogens already today [7-10].

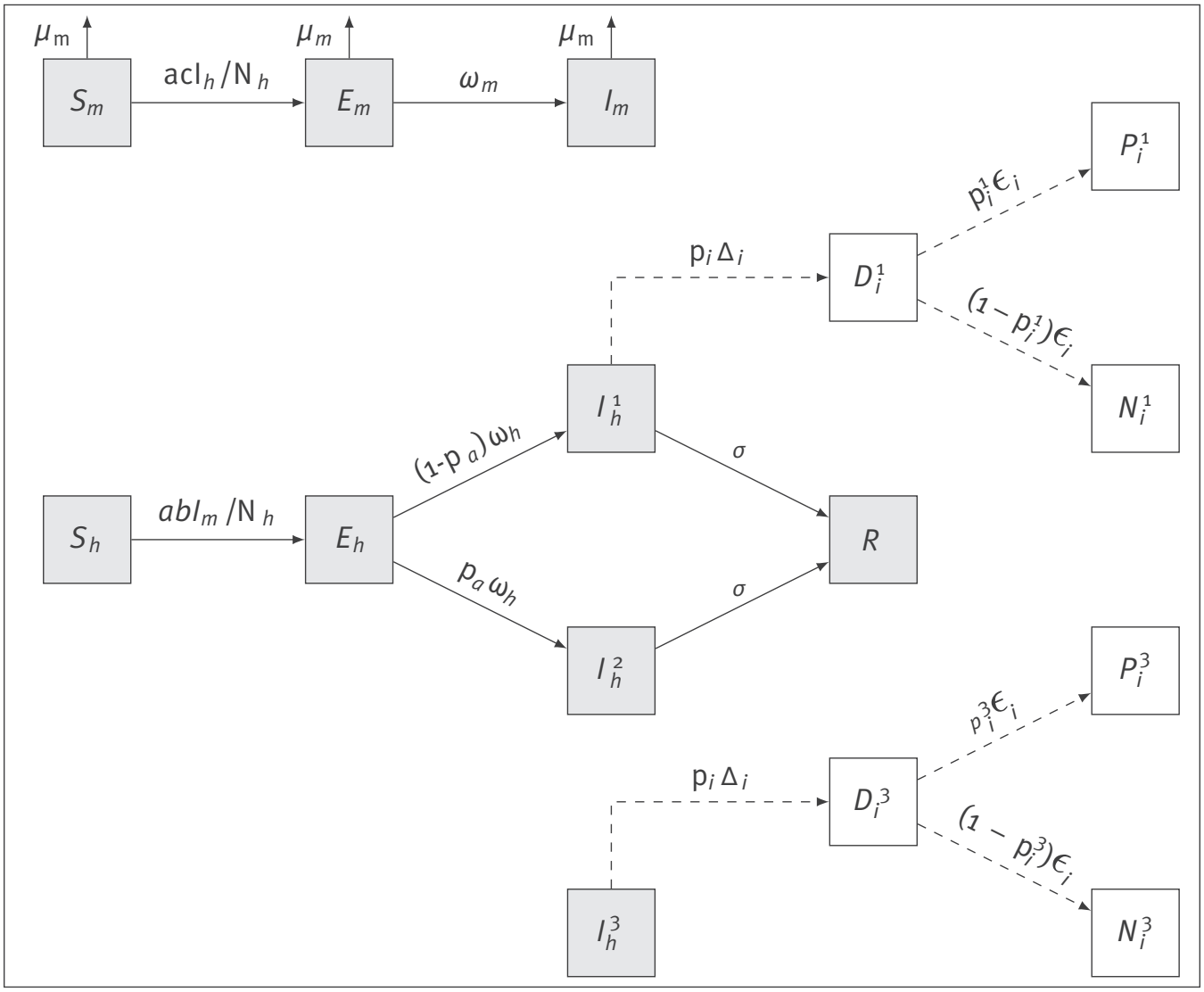
This risk of disease transmission by invasive vectors was particularly significant in 2014. Indeed, the occurrence of a large chikungunya outbreak on several Caribbean islands [11-13] during the season of *Aedes albopictus* vector activity in southern France [14] became problematic for public health risk management because of the high number of imported cases recorded [15]. While virus transmission remained under control in 2014, with moderate local transmission of dengue and chikungunya viruses [16], this situation can be expected to repeat in the future and requires an efficient public health strategy rooted in quantitative risk assessment under the current and alternative strategies.

For chikungunya virus, the current strategy in vector-infested areas and during the season of vector activity comprises the following components [15]: Suspected cases (defined by the presence of acute fever and joint pains not explained by another medical condition) are immediately reported to public health authorities. Such cases are then confirmed by serology (IgM-positive or a fourfold increase in IgG titre) or detection of viral nucleic acids in plasma by real-time reverse-transcription PCR (RT-PCR).

If the suspected case is imported from a chikungunya-endemic or -epidemic area, vector control (VC) measures, such as spraying adulticides to temporarily reduce the density of adult mosquitoes and removing stagnant water to decrease the number of breeding sites, are implemented within 200 m of the places in mainland

Figure 1

Structure of the mathematical model assessing public health strategies again chikungunya virus transmission, mainland France



France visited by the patient during the likely viraemic period (from the day before until seven days after the onset of symptoms), without waiting for laboratory confirmation. In the absence of proof of local transmission (i.e. without any previous biological confirmation of an autochthonous case), VC measures around suspected autochthonous cases are delayed until these cases are laboratory-confirmed.

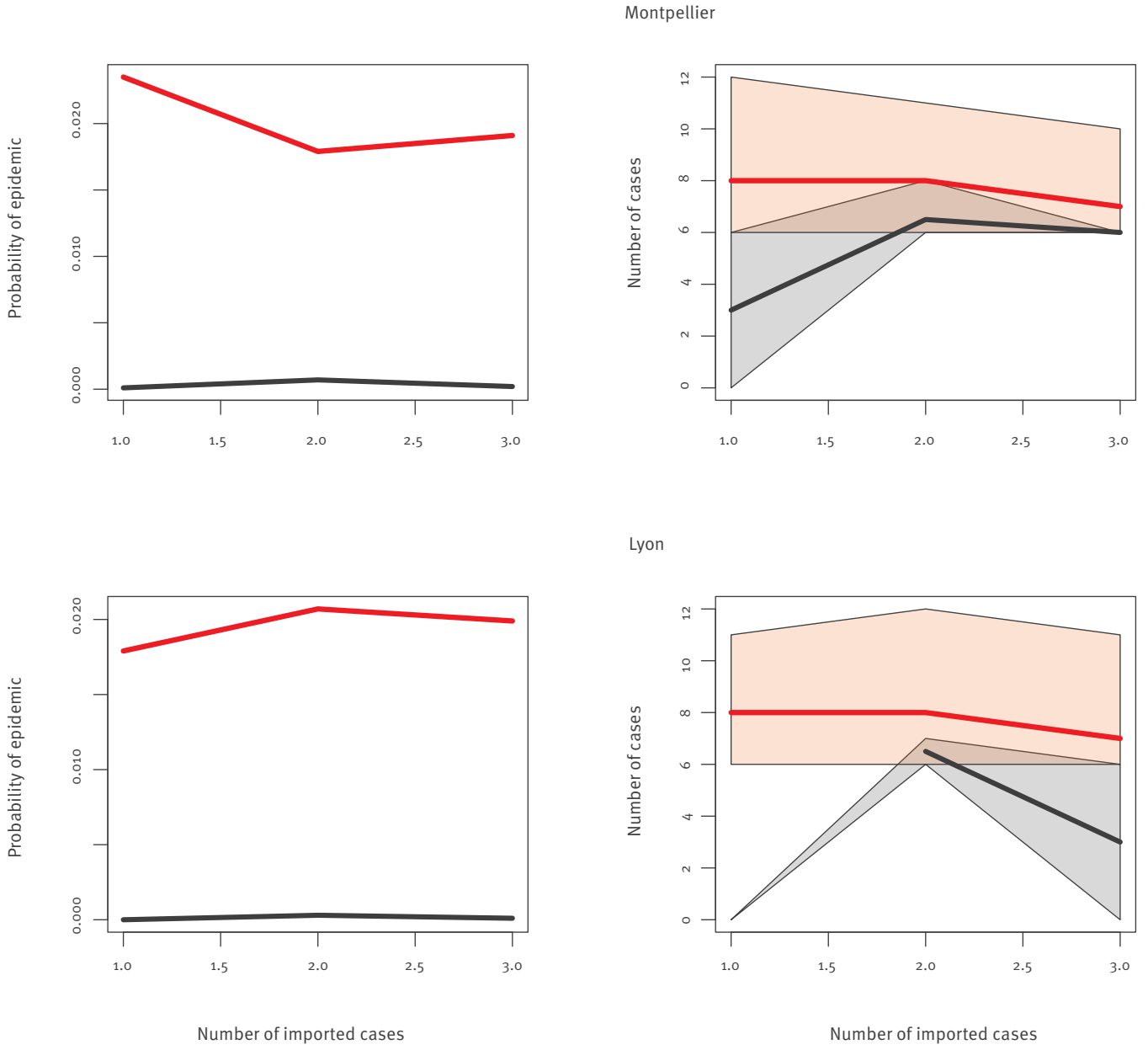
The notification of a laboratory-confirmed autochthonous case triggers immediate epidemiological and entomological investigations and control measures, including active case finding in the neighbourhood of the case's residence and in other areas visited by the case. VC is then implemented around the confirmed cases and around any further suspected autochthonous cases.

One of the main questions is whether or not waiting for laboratory confirmation is relevant before implementing VC locally. Intuitively, the most efficient strategy in epidemiological terms would be to implement VC as soon as possible, i.e. just after the notification of a clinically suspected case, whether the case is imported or locally acquired (autochthonous). However, the number of false notifications (clinical suspicion of chikungunya cases where chikungunya virus is not involved) is substantial because of the low specificity of the symptoms: in 2015, only six cases were confirmed among 532 notified cases (personal communication: Alexandra Septfons, INVS, April 2015). Therefore, the efficiency of such strategies has to be assessed. In order to design the most efficient public health strategy, it is important to quantify how many secondary cases occur because VC is delayed until laboratory confirmation for the suspected imported and autochthonous cases.

We designed a mathematical model for chikungunya control, which could be easily extended to other

Figure 2

Modelled probability of epidemics (defined as simulation with at least five local cases) and number of autochthonous cases (in simulations identified as epidemic) in simulations without vector control



Red lines: maximum mosquito density (800 females/ha); black lines: minimum density (20 females/ha). The confidence intervals are the 95% interval over the 10,000 simulations defined by the 2.5th and 97.5th percentiles.

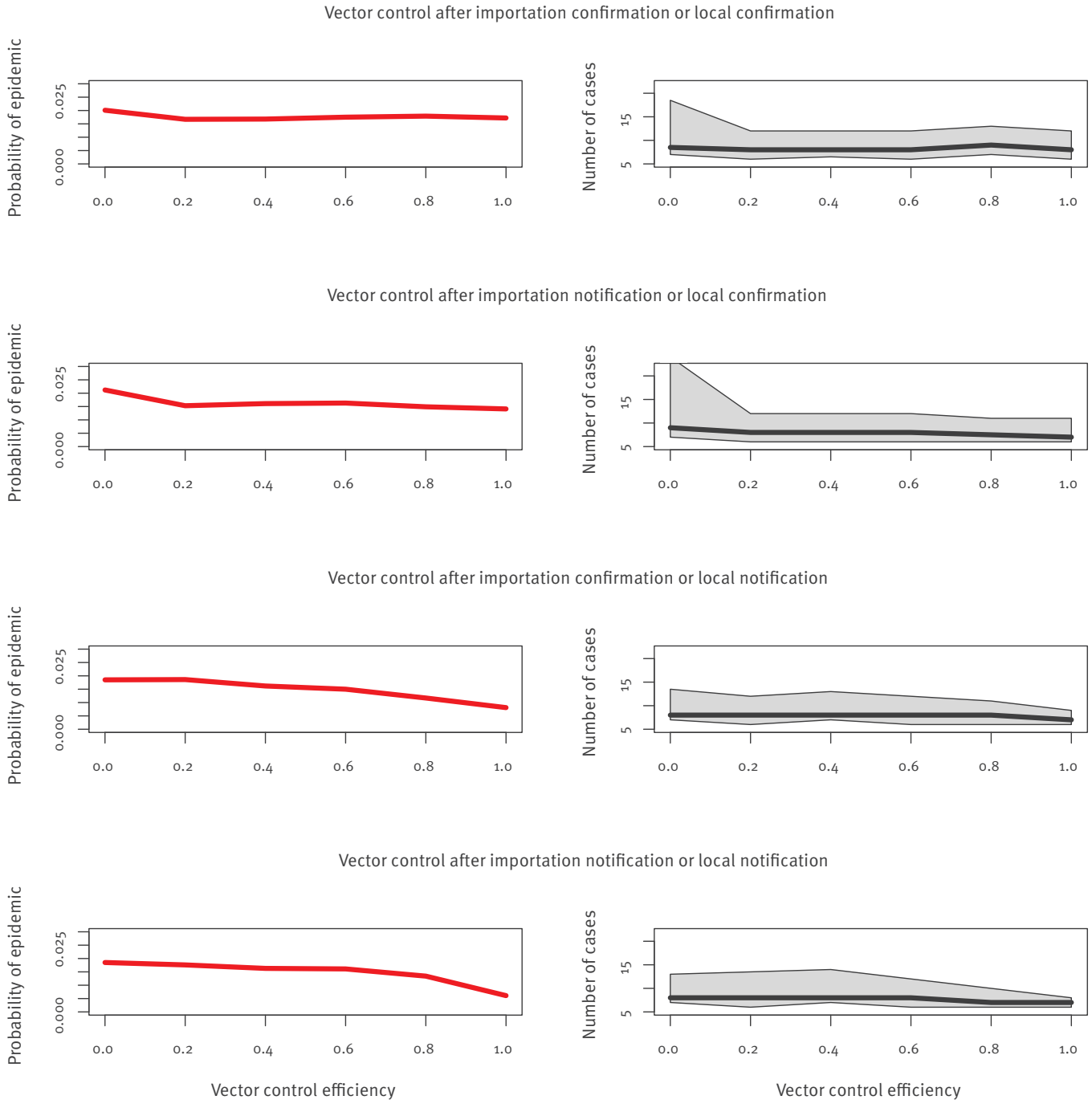
vector-borne diseases (e.g. dengue or Zika virus infections) and/or surveillance systems, in order to analyse theoretically four possible public health strategies (VC after clinical suspicion or after laboratory confirmation, for imported or autochthonous cases). We include in this model the surveillance data obtained during the 2014 season, suggest what could be the optimal strategy for the following years and make recommendations how to improve the surveillance system.

Methods

We developed a stochastic epidemiological model [17] rooted within the SIR (susceptible-infectious-recovered) framework where populations of humans and vectors are compartmentalised according to their infection status (Figure 1). Human individuals start simulation in a susceptible state (S_h) and then can be infected through bites of infectious vectors (I_m) at rate a and with the probability b. When infected (E_h), these individuals become, at a rate ω_h, infectious and symptomatic (I_h^1) with the probability $(1 - p_a)$, or asymptomatic (I_h^2) with the probability p_a. Finally, infectious individuals

Figure 3

Impact of vector control strategies on probability of epidemics (defined as more than three locally acquired cases) and number of locally acquired cases after importation of one case

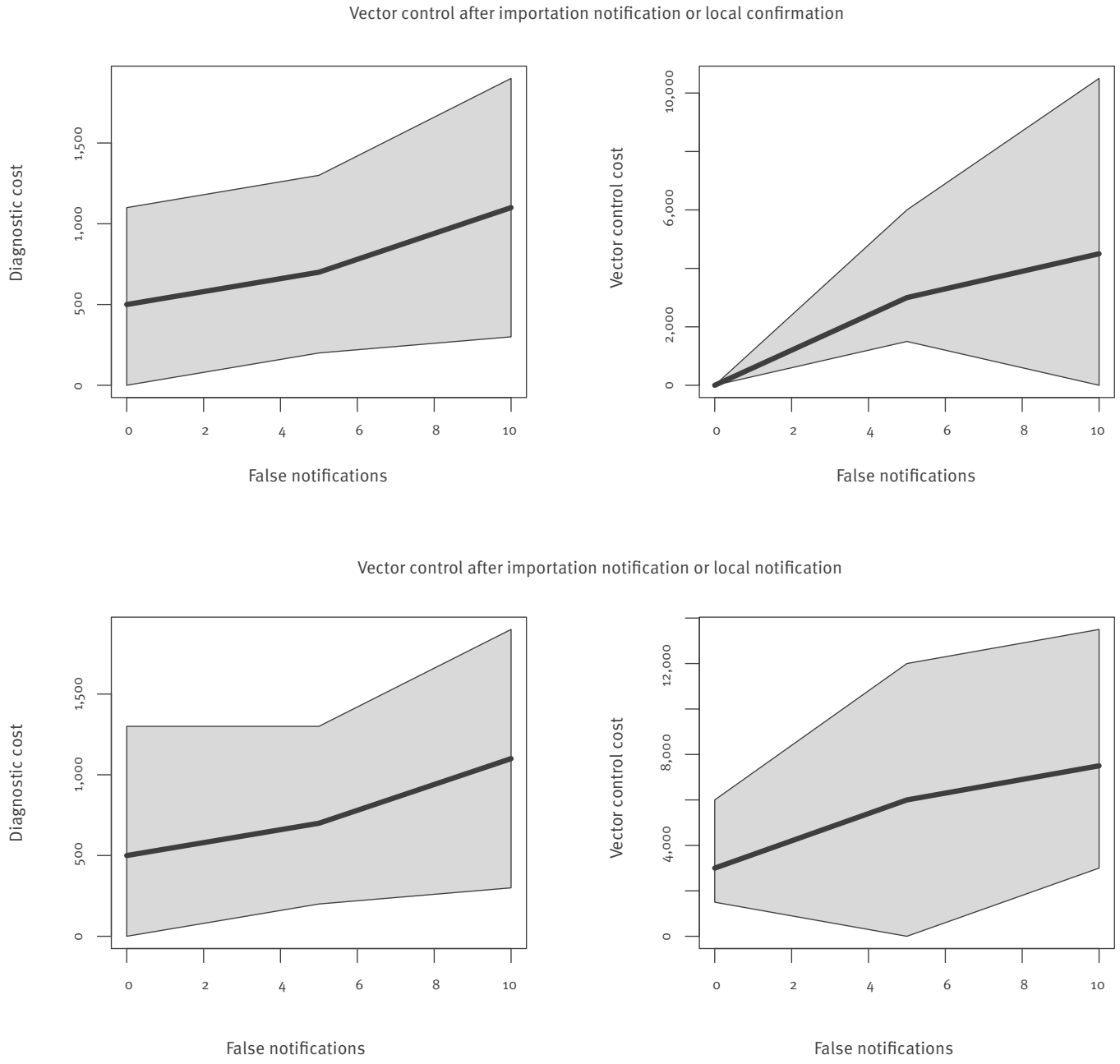


Solid lines represents the median of the simulations.

While starting vector control (VC) after suspicion or confirmation of an imported case did not significantly change the epidemiological outcomes, implementing VC immediately after the notification of a suspected locally acquired case rather than awaiting laboratory confirmation allowed the greatest reduction in the probability of an epidemic. The efficiency of VC represents the percentage of the vector population that was removed by VC operations.

Figure 4

Costs of diagnostics (left panels) and vector control (right panels) by number of false notifications



Top panels: vector control (VC) triggered after biological confirmation; bottom panels: VC triggered only after suspicion. Costs are in EUR/ha.

become recovered (R) at rate σ and cannot be infected again. Similarly, if a susceptible mosquito vector (S_m) bites an infectious human (I_h^1, I_h^2) at rate a, the mosquito can become infected (E_m) with the probability c and then infectious (I_m) at the rate ω_m, characterised by the inverse of the extrinsic incubation period.

In order to quantify the direct economic costs of false notifications of autochthonous cases to the health system, a third class of individuals (I_h^3) was considered which represented non-infected individuals who appear symptomatic. These erroneous suspicions may trigger VC if laboratory diagnostic is not required a priori. Furthermore, laboratory tests may return false-positive results, resulting in erroneous confirmation and autochthonous case notification, triggering VC implementation.

A sub-model considering specifically the case detection and diagnosis process was added on top of this epidemiological framework. When a new individual is added (through importation or local contamination) to

Table

Parameters used in the model assessing public health strategies again chikungunya virus transmission, mainland France

Parameters	Description	Values	Source
Diagnostics and vector control			
p_i	Proportion of each diagnostic method	0.29; 0.29; 0.42	INVS[a]
p_i^3	Proportion of false positives for each method	0.027; 0.05; 0.05	INVS[a]
$1 - p_i^1$	Proportion of false negatives for each method	0.03; 0.03; 0.03	INVS[a]
ε_i	Confirmation rate for each method	6; 7; 14 days per individual	INVS[a]
Cost for each diagnostic		EUR 200; 100; 100	Arbitrary values[b]
Cost of Vector control		EUR 1,500	Arbitrary value[b]
Pathogen			
σ	Recovery rate	4 days per individual	[20]
a	Biting rate of vector species	0.25 days per individual	Arbitrary value (no study exists today on *Aedes albopictus* in southern France)
μ_m	Vector mortality rate	19 days per individual	[27]
b	Infection probability of a susceptible human exposed to the pathogen	0.3	Arbitrary value[b]
c	Infection probability of a susceptible mosquito exposed to the pathogen	0.3	Arbitrary value based on a virus poorly adapted to the local mosquito ([22] suggests 0.6 in a well-adapted environment)
Θ	Efficiency of vector control	Variable	Variable
ω_h	Incubation rate in the human host	3 days per individual	[22]
Ω_m	Incubation rate in the mosquito	2days perindividual	[22]
Δ	Physician consultation rate when infectious	6days per individual	INVS[a]
p_A	Proportion of locally acquired cases not detected (including asymptomatic)	0	Arbitrary value[b]

INVS: Institut de Veille Sanitaire (French Institute for Health Surveillance).

[a] Values from INVS cover the whole 2014 season in France and have been averaged over this season.

[b] All arbitrary values have been decided in consultation with the Centre National d'Expertise des Vecteurs.

the number of individuals in class I_h^1 (truly infected) or in class I_h^3 (wrong suspicion; individual not infected with chikungunya virus), the number of individuals ready for laboratory tests (class D_i^1 or D_i^3) will increase at a rate Δ_i, where Δ_i represents the notification period of the diagnostic method *i*. The diagnostic methods considered here are PCR confirmation and serology. Each diagnosis is executed at rate ε_i (representing diagnostic time) and the suspected cases can become confirmed (P_i^j) or reversed (N_i^j) with the probability p_i^j or $(1 - p_i^j)$ respectively. For the diagnostic method *i*, $(1 - p_i^j)$ represents the proportion of false negatives when $j=1$ (real infectious individuals), while p_i^j represents the proportion of false positives when $j=3$ (false notification). Finally, each diagnostic method has an associated cost in order to estimate the total direct cost for biological confirmation.

Finally, VC can be implemented when D_i^j increases by 1 (i.e. when a new infected individual is detected) if the strategy is to implement VC after suspicion ($j=1$ represents real infection while $j=3$ represents erroneous notification). If the strategy is to await laboratory confirmation for both locally acquired and imported cases, VC will be implemented when P_i^j increases. Tracking the changes allows us to address the four possible strategies, namely implementing VC after clinical suspicion and/or after laboratory confirmation for autochthonous and/or imported cases. VC is based on an integrated approach (source reduction, social mobilisation for destruction of breeding sites such as stagnant water, as well as ultra-low volume (ULV) and thermal fogging for control of adult mosquitoes). Based on experience with mosquito control operators and the biology of *Ae. albopictus* in temperate areas, we considered that the mosquito population decreases by θ%, representing the efficacy of VC, during 10 days. After this period, the mosquito population recovers its previous level. Finally, we assumed that a VC operation has an average cost and that the total VC cost is the sum of all VC operations implemented multiplied with this average cost. Details on all transition events can be obtained from the corresponding author and are also available at https://sites.google.com/site/rocheben/sochakiEtAlAppendix_V3.docx*.

For each studied scenario, we replicated 10,000 simulations through the Gillespie's direct method [18]. In order to have a mosquito population that could be fully reached by VC, we considered a very fine spatial scale

of one hectare. Similarly, we simulated one single season (six months) because we were focussing here on the short-term impact of the VC strategies. Over this single season, the number of imported cases, which could be of different infectious status, were assumed to arrive uniformly in the population (e.g. one imported case at the beginning, one imported case in the middle and one at the end of the season, if we consider three imported cases). We considered two specific situations for the vector density (ranging from 20 to 800 females per hectare [19]), and two human densities corresponding to the cities of Montpellier and Lyon (46 and 102 inhabitants per hectare, respectively) which are both exposed to increasing vector abundance. All parameters are detailed in the Table and are estimated at the spatial scale of one hectare. Finally, throughout the manuscript, we focus on the probability of the establishment of a local transmission chain (defined as the occurrence of more than five autochthonous cases), called the probability of epidemic, and on the number of autochthonous cases during an outbreak.

Results

Based on this model, we could derive the basic reproductive number (R_0) that quantifies the number of secondary infections that arise when a single infective host is introduced in a fully susceptible host population. Based on previous results from a chikungunya outbreak in Italy [20], we characterised the R_0 as:

Formula 1

$$R_0 = \frac{N_V}{N_h}\,\frac{bc}{\sigma\mu_m}\,\frac{\omega_m}{\omega_m+\mu_m}$$

Based on the parameters detailed in the Table, we consider in this study R_0 values ranging from 0.16 to 6.72 in Montpellier and from 0.07 to 2.99 in Lyon (according to vector and human densities), which is consistent with current estimations [20].

In order to quantify the net epidemiological impact of imported infectious individuals, we first considered a simple case without VC but with perfect tracking of infectious individuals (no asymptomatic cases nor false notification). As could be expected, we found that an increasing vector density significantly increased the probability of an epidemic (Figure 2), from 0% to 2%, and therefore the size of the epidemic (number of locally acquired cases). However, the number of imported cases had a very weak impact on the probability of an epidemic, from 0% to 0.1% for low vector density, yielding a large confidence interval for the size of the ensuing epidemic because the smaller number of simulations on which size of the epidemic could be calculated.

Based on the high vector density in Lyon (with a R_0 of 2.99), we then focused on the four possible strategies that could be implemented, namely implementing VC (i) after notification of clinical suspicion of imported case(s) and laboratory confirmation of autochthonous transmission, (ii) after laboratory confirmation for either imported or autochthonous cases, (iii) after laboratory confirmation of an imported case or after clinical suspicion of an autochthonous case without laboratory confirmation or (iv) after a clinically suspected case, either imported or autochthonous. VC efficacy had a considerable influence on epidemiological outcomes, although the impact was stronger on the probability than on the size of epidemics (Figure 3).

Our model shows that not all strategies are equivalent. While the size of the epidemic remained roughly similar across the strategies, the probability of an epidemic was reduced when VC was started as soon as autochthonous transmission was suspected, without awaiting laboratory confirmation of cases. Starting VC upon suspicion or after confirmation of imported cases did not alter the epidemiological outcome.

Assuming a VC efficacy of 80% and one imported case within the area, we focused on direct economic costs of the two strategies for autochthonous cases. For this, we introduced non-infectious individuals (I_h^3) who nonetheless were entered in the surveillance system through erroneous suspicion and tested for laboratory confirmation (with the possibility of false positives). Figure 4 shows that the cost of VC increased significantly when VC was implemented after suspicion of cases rather than after their confirmation. However, the impact on diagnostic cost was weak.

Discussion

This first theoretical exploration chiefly aimed to highlight the various factors influencing the probability of a chikungunya epidemic and its spread in southern France and to show the possible consequences of different public health strategies. In this work, we considered four strategies: (i) VC after suspicion of an imported or autochthonous case, (ii) VC after suspicion of an imported case or after confirmation of a locally acquired case, (iii) VC after confirmation of an imported case or suspicion of autochthonous transmission or (iv) VC after confirmation of an imported or locally acquired case. We found that implementing VC immediately after notification of a suspected case did not significantly change the size of the epidemic, compared with delaying implementation of VC until laboratory confirmation. In other words, awaiting confirmation before implementing VC is not expected to result in a larger epidemic (with the current notification delay). However, our results suggest that awaiting laboratory confirmation before implementing VC around autochthonous cases may result in higher probability of an epidemic. However, the optimal strategy is also subject to economically constraints. In our model, implementing VC readily after suspicion was more expensive than after laboratory confirmation because of erroneous suspicions. Moreover, repeated VC operations are generally not feasible in the field for logistical

reasons and concerns of the population about repeated insecticide spraying.

The fact that the different strategies for imported cases did not significantly change the probability of an epidemic or its size, was mainly due to the delay between the infectious individuals entering the surveillance system and the notification of these imported cases. In 2014, this delay was six days on average, i.e. when the infectious individual has almost finished their infectious period and had potentially transmitted the virus to local *Aedes* mosquitoes. In addition, we observed that this delay had to be decreased significantly if we aimed to decrease significantly probability of epidemic following the introduction of imported cases (data not shown; details can be obtained from the corresponding author and are also available at https://sites.google.com/site/rocheben/sochakiEtAlAppendix_V3.docx*).

Some assumptions made by this model deserve to be discussed. Firstly, some epidemiological parameters were unknown and were fixed arbitrarily. This is especially relevant for the probability that a susceptible vector gets infected after biting an infectious human (parameter *c*). Indeed, the vector competence of *Ae. albopictus* populations in Metropolitan France will depend on the chikungunya strain infecting the human population and therefore on the geographic origin of the imported case. Nevertheless, we have conducted a sensitivity analysis (details can be obtained from the corresponding author and are also available at https://sites.google.com/site/rocheben/sochakiEtAlAppendix_V3.docx*), in which our main conclusions remained valid for a large range of parameters. Secondly, our estimated costs, for both diagnostics and VC, allowed to compare between the different scenarios but they underestimated the real costs since only direct costs were included. Finally, we considered here a very fine spatial scale (one hectare). As a consequence, we neglected the important component of human movements. The situation described here corresponds to outbreaks very localised in space, for which this scale is relevant. Nevertheless, in the case of a more diffuse outbreak, this model would need to be extended to a broader scale.

An important result arising from our paper is the influence of vector density on both probability and size of epidemics. While this result could have been expected based on the existing literature [17,21], it is nevertheless worth pointing out that such a relationship is strongly dependent on how the transmission force between vector and hosts is modelled. Here, we used the most popular way of vector-borne disease modelling (asymmetric frequency-dependent transmission). However, we could also show that another way of modelling this transmission force, through a symmetric frequency-dependent process, can result in the absence of a relationship between vector density and size of the epidemic (data not shown; details can be obtained from the corresponding author and are also available at https://sites.google.com/site/rocheben/sochakiEtAlAppendix_V3.docx*), as empirical data suggest for dengue [22]. Nevertheless, the only qualitative change arising with this other kind of transmission force is the influence of vector density. Therefore, although we cannot draw a definite conclusion regarding the influence of vector density, the main conclusion (implementing VC after suspicion for autochthonous cases is the best way to reduce the consequences of an epidemic) remains valid.

Other modelling studies have focused on chikungunya virus transmission in other epidemiological settings [20,23,24], some with a focus on VC [25]. Some studies have highlighted that certain areas are more suitable than others for chikungunya epidemics [26]. Nevertheless, this study is as far as we know, the first to focus on such concerns (large number of imported cases combined with local presence of vector) in Europe. While specifically designed the model to mimic the French surveillance system, we believe that it can easily be adapted to other surveillance systems.

It is worth pointing out that the outcomes of our model matched the size of the epidemic observed in Montpellier in 2014 [15] where 11 autochthonous cases were recorded after the introduction of a single imported case. While such agreement cannot validate the whole framework on its own, it nevertheless underlines that the approach is worth exploring and may provide useful insights for public health strategy.

The current strategy in France foresees the implementation of VC after suspicion of imported cases or after confirmation of autochthonous cases. Nevertheless, when local transmission is proven, current strategy assumes that VC is applied around every suspected autochthonous case without awaiting laboratory confirmation. This strategy is used because imported cases are relatively easy to discern (travel in an endemic area) and the positive predictive value of the clinical case definition is higher in this high-prevalence population group. Conversely, the low predictive power of the clinical case definitions in the resident human population that has not travelled to endemic areas leads to reporting of many patients not infected by chikungunya virus, creating high costs for unnecessary interventions. Overall, our theoretical framework suggests that such a strategy, in the current conditions (and especially with the current delay in case reporting), could be the most efficient one, both in economic and epidemiological terms, if proof of local transmission can be established rapidly enough. The model developed here aimed to be as generic as possible, so that it can be used as a general framework to test other scenarios or to analyse VC strategies for other diseases.

*Note

Supplementary information made available by the authors on an independent website is not edited by Eurosurveillance,

and Eurosurveillance is not responsible for the content. The material can be accessed at: https://sites.google.com/site/rocheben/sochakiEtAlAppendix_V3.docx.

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Conflict of interest

None declared.

Authors' contributions

BR, DF, FS and MCP have designed the study. TS and BR did the modelling analysis. FJ and YP have improved the entomological component of the model. HN, MCP AS improved the surveillance component of the model and analysed the surveillance data during the 2014 season. All authors have significantly contributed the writing of the manuscript.

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