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Pierre-Yves Boëlle, Guy Thomas, Elisa Vergu, Philippe Renault, Alain-Jacques Valleron, Antoine Flahault

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Investigating transmission in a two waves epidemic of Chikungunya fever, Réunion Island

P.-Y. Boëlle[1]

G. Thomas[1]

E. Vergu[2]

P. Renault[3]

A.-J. Valleron[1]

A. Flahault[1]

1 - Université Pierre et Marie Curie-Paris6, UMR S 707, Paris, F-75012 ; INSERM, UMR-S 707, Paris, F-75012 ; AP-HP, Paris, F-75012

2- INRA MIAJ, Jouy en Josas, France

3-CIRE Réunion Mayotte, DRASS Réunion, Saint-Denis, F-97408

Corresponding Author :
Pierre-Yves Boëlle

Unité de Santé Publique

Hôpital Saint-Antoine

184, Rue du Faubourg Saint-Antoine

75012 PARIS

e- mail : boelle@U707.jussieu.fr

Phone : (33) 1 49 28 32 26 / Fax (33) 1 49 28 32 33

Running Head: Reproduction number of Chikungunya fever

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Abstract

An epidemic of Chikungunya fever, a mosquito borne viral disease, spectacularly swept through Réunion Island (population 780,000) in 2005-2006. There were 3000 cases in a first wave (March to June 2005) and more than 250,000 cases in a second (December 2005 to April 2006). Adapting newly developed epidemiological tools to vector borne diseases, we show that despite this massive difference in magnitude, the transmission potential as measured by the number of secondary cases per index case (or reproduction number), remained similar during the two consecutive waves. The best estimate for the initial reproduction number R_0 was 3.7, with a possible range from 2 to 11 depending on incubation duration and lifespan of the mosquito. We conclude that an increase in virulence between the two seasons was not necessary to explain the change in magnitude of the epidemics, and that the attack rate may be well over 50% in Chikungunya fever epidemics in the absence of intervention.

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Introduction

Chikungunya fever, a mosquito borne viral (*or* arboviral) disease, was first described in 1953(Ross 1956). Sporadic epidemics have been reported in Africa and Asia, interspersed by years of silence(Laras et al. 2005). Lately, Chikungunya fever was active again in East Africa and the Indian Ocean(Schuffenecker et al. 2006). The disease entered Reunion Island, a French territory in the Indian Ocean, in February 2005, and was still active by September 2006. The epidemic was all the more spectacular as 250,000 cases were observed between December 2005 and April 2006, bedwarfing an initial outbreak of 3000 cases from March to June 2005. The existence of molecular changes in the virus have been proposed to explain this massive increase in incidence(Schuffenecker et al. 2006).

To investigate this issue, as well as the likelihood of future epidemics, it is required to determine the transmission potential of the disease. This may be efficiently summarized by the number of secondary cases per each index case, or reproduction number R(Anderson and May 1991; Roberts and Heesterbeek 2003): indeed, more than one secondary case by index case (R>1) corresponds with an epidemic situation, while R<1 leads to disease extinction. In directly transmitted diseases, the value of the reproduction number during the epidemic may be calculated from little information: the epidemic curve, and the "generation interval", *i.e.* the period between an index case symptoms and that of his/her secondary cases(Fine 2003; Wallinga and Teunis 2004). The epidemic curve was available almost in real time from the local health authorities in Réunion Island, with daily incidence of laboratory confirmed cases before December 2005, and weekly incidence extrapolated from a network of GPs afterwards(Paquet et al. 2006), but the generation interval (GI) distribution is unknown for Chikungunya fever. A subset of traced secondary cases would allow estimation of the GI along with the reproduction number(Cauchemez et al. 2006), but, direct tracing of transmission is impractical in mosquito transmitted diseases. However, the components of the

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generation interval, comprising the incubation and infectious periods in the host followed by the cycle of transmission by mosquitoes, are well documented(Peters and Dalrymple 1990). More specifically in a vector transmitted disease, an index case is an infected individual who infects a susceptible mosquito, while a secondary case is a susceptible person who is infected by an infected mosquito. In addition to the three time periods determining the GI in directly transmitted diseases (time from infection to infectiousness, duration of infectiousness, time from infection to clinical onset), the interval between the virus leaving its infectious host and entering a susceptible host must be taken into account.(Fine 2003)

Here, after determining the temporal profile of the reproduction number for the Chikungunya epidemic in La Réunion during the two consecutive epidemic waves, we finally conclude on the likelihood of a change in virulence and on the likelihood of future Chikungunya fever epidemics.

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Methods

Gonotrophic cycles and Chikungunya transmission

Several mosquito species may become infected and transmit the Chikungunya virus(Peters and Dalrymple 1990). In Réunion Island, the principal vector was *Aedes albopictus*(Reiter et al. 2006). Transmission of the disease must be understood according to the gonotrophic cycle (GC) in the mosquito, that is the process of blood-feeding, egg maturation and oviposition[laying eggs].(White 1987) Schematically, female mosquitoes take one blood meal, then produce and lay eggs in each gonotrophic cycle. We use this fact in reconstructing the generation interval.

Determination of the generation interval

A framework for calculating the GI in directly transmitted diseases was proposed earlier, that we adapt to vector borne diseases(Fine 2003) (Figure 1). In this framework, the generation interval $T = -T_V + T_B + T_M + T_I$ has four components which we detail below (see Table 1 for all notations):

- T_V is the time from infectiousness to symptoms in the human host. We assume that infectiousness starts with detectable viremia. This occurs during the 2 days preceding symptoms onset for Chikungunya fever(Peters and Dalrymple 1990).,We choose T_V to be 1 day with probability 2/3 and 2 days with probability 1/3.

- T_B is the time from infectiousness in a human host to a mosquito bite infecting the insect. We assume that biting may occur anytime during the viremic period in the human host. T_B is therefore uniform on 1 to 6 days(Peters and Dalrymple 1990).

- T_I is the time from infection to symptoms in a human host. In most individuals this is 2-3 days, but may be longer than 6 days in 5% individuals(Paquet et al. 2006; Peters and Dalrymple 1990). T_I was assumed lognormal with mean 3 and standard deviation 1.3, so that 95% of the expected values were between 1 and 6 days.

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- T_M is the time between infection of the mosquito and a subsequent bite infecting a human host. As outlined above, this must be a multiple of the average GC duration, which was 4 to 6 days under similar latitudes (Mori and Wada 1977).

Two additional parameters are required to determine the GI probability distribution function. First, a latency period may be present in the mosquito, and we denote K_{MIN} the index of the first GC following infection where transmission becomes possible. $K_{MIN} = 1$ means that transmission is possible in the first GC following infection. Second, the probability that a mosquito may live and bite must decrease with the number of GCs since infection. We therefore assigned a decreasing weight π_k to the k-th GC after infection in the form $\pi_k(\rho) \propto (1-\rho)^{k-K_{MIN}}$ with $0 \leq \rho \leq 1$, so that the first GC where transmission was possible had weight 1. The extreme case $\rho = 0$ allows equal contribution to transmission of all GCs after latency, leading to a long infectious lifespan for the mosquito. On the contrary, $\rho = 1$ effectively limits transmission to the first GC after latency, leading to a short infectious lifespan. We limited the total number of GC for transmission to 8 (corresponding to a maximum infectious lifespan of 40 days), and rescaled the π_k's so that $\sum_{k=K_{MIN}}^{8} \pi_k = 1$.

A Monte-Carlo algorithm was used to calculate the distribution of the generation interval for Chikungunya fever for several values of K_{MIN} and ρ. (See Appendix)

Epidemic curve

We used incidence data for the period from the 8th week of 2005 (last week of April) to the 10th week of 2006 (mid March). All data were provided by the local health authorities (CIRE Réunion) as weekly incidence counts. Up to the end of 2005, incidence was calculated from the number of suspected cases (defined by sudden fever and arthralgia) confirmed by antibody testing or viral isolation. Afterwards, weekly incidence was extrapolated from the cases reported by a sentinel network of 31 GPs (see Appendix). Weekly reports by the health

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authorities are available on the web site of the InVS (French Center for Disease Control) for the whole epidemic period. (http://www.invs.sante.fr/chikungunya).

Determination of the reproduction number

If all cases were traced to their index case, the weekly reproduction number could be computed as the average number of secondary cases during each week. In the absence of case tracing, the reproduction number may however be determined if an index case is imputed for each new incident case. This imputation must be made proportionally to the GI probability distribution function(Wallinga and Teunis 2004). More precisely, the probability p_{jk} that a case with symptoms during week k was infected by a case with symptoms during earlier week j is evaluated as(Cauchemez et al. 2006):

$$p_{jk} = \frac{w(k-j)}{\sum_i (n_i - \mathbf{1}\{i=k\}) w(k-i)}$$

where $w(.)$ is the probability density function of the GI, n_i the incidence of symptomatic cases in week i, and $\mathbf{1}\{i=k\}$ is 1 if i=k and 0 otherwise. The decrease by 1 is necessary since a case may not have been its own index case. Finally, the mean reproduction number for cases seen in week j is $R_j = X_j/n_j$, where $X_j = n_j \sum_k (n_k - \mathbf{1}\{k=j\}) p_{jk}$ estimates the total number of secondary cases from cases with onset in week j. The initial reproduction number, or R_0, may be obtained as an average over the first weeks of the epidemic: here we used the four first weeks.

Posterior validation

Given the reproduction number for each week and the probability distribution function of the GI, surrogate epidemics may be obtained by computer simulation. This provides a natural way to evaluate how a particular combination of reproduction number temporal profile and GI distribution capture the features of the observed epidemic curve. For each combination of K_{MIN} and ρ, we calculated a GI distribution and obtained the temporal profile of R using the

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method described above. One thousand surrogate epidemics were then simulated for each GI and corresponding R profile. The distance between the weekly observed incidence (n_t) and corresponding average incidence over all surrogate epidemics (En_t) was evaluated by $\sum_t \frac{(n_t - En_t)^2}{En_t}$. This measure is a score function based on a Poisson distribution for n_t with mean and variance En_t.

Surrogate epidemic curves $\{n_t^*\}$ were simulated with the following algorithm:

- Initialize (n_1^*, n_2^*, n_3^*, n_4^*) to (n_1, n_2, n_3, n_4), the number of cases observed in the Réunion epidemic in the first four weeks (week 9 to 12 of 2005),

Then, for all t,

- Sample X_{t+1} from a Poisson law with mean $n_t \times R_t$. This is the number of new cases caused by those with onset in week t.
- Obtain X_{t+1} durations by independent sampling of the GI distribution. These are the generation intervals for the new cases.
- Update $\{n_t^*\}$ by allocating the X_{t+1} new cases to the dates of symptoms

Epidemics were simulated on a grid of 21 values for ρ spanning the interval from 0 to 1, and 4 values of K_{MIN} from 1 to 4.

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Results

Generation interval

Figure 2 illustrates the variety of generation interval distribution obtained by the method described above. Varying ρ, the GI could span from 1 to 8 weeks: the range was shorter with large values of ρ and increasing K_{MIN}. In the following, we reported six cases illustrating various latency periods (K_{MIN}=1, 2, 3; corresponding to <5 days, <10 days and <15 days latency), and extreme conditions for mosquitoes' average infectious lifespan (ρ=0 long lifespan, ρ=1 short lifespan).

Temporal pattern of the reproduction number

The temporal patterns of the reproduction number were similar irrespective of hypotheses: R was the largest in the early phases of the epidemic (April 2005), decreased as the austral winter set in (Figure 3), then rose again during spring (September – November), and reached high levels in January 2006. The values taken by the reproduction number changed with the value of ρ and the value of K_{MIN}. Small values of ρ, yielding a long GI, were associated with larger values of R.

For ρ=0, the initial reproduction number R_0 was 6.0 (average of 6.9, 5.5, 5.5, 6.2), 8.4 (average of 9.2, 7.3, 8.2, 8.8) and 11.0 (average of 10.9, 10.0, 11.3, 12.0) as K_{MIN} increased from 1 to 3. With ρ=1, yielding a shorter GI, the corresponding values were reduced to 2.1 (average of 2.1, 0.9, 1.1, 4,5), 3.4 (4,4 , 0.9, 2,3, 6,2) and 4.5 (3,5, 1,9, 4,3, 8,4).

We estimated the number of mosquitoes infected by a human host by the ratio of the reproduction number to the average number of cycles in the generation interval. In the week with the highest reproduction number, this coincided with the maximal values of R for ρ=1 (3.9, 6.2 and 8.3), and was 0.9, 1.4 and 2 for increasing values of latency (K_{MIN}=1, 2, 3). Given the duration of the viremic period (up to 7 days) this represented less than one mosquito infecting bite per day.

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In a particular week, the dependence of R on ρ was smooth but not linear, as illustrated by Figure 4 for the case of K_{MIN}=2. This figure shows that the R profiles remained very similar over the whole range of ρ values, with changes the most pronounced during the epidemic periods.

Posterior validation

As illustrated by Figure 2, a large variety of GI distributions were possible in our framework. In Figure 5, the mean predicted epidemic is shown for the six GI instances described above, together with the observed epidemic in the first season. In the absence of a latency period in the mosquito (K_{MIN}=1), the simulated epidemics tended to be too small. In other cases, the fit was good, although the epidemic tended to be over smoothed with longer GIs. Table 1 provides a summary of the distance between simulated outbreaks and the observed outbreak. We found that the distance from simulated to actual epidemic decreased with large values of ρ, with a minimum at K_{MIN}=2 and ρ=0.95. In this case, the initial reproductive number was 3.7; the epidemic profile obtained by posterior validation was very similar to the case presented in Figure 3 with K_{MIN}=2 and ρ=1.

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Discussion

By mid 2006, the temporal pattern of the reproduction number of Chikungunya in Réunion Island has presented two peaks preceding the epidemic waves. The initial reproduction number was between 2 to 11, with a best fit at 3.7. It is noteworthy that while the two epidemic waves differed widely in scale (thousands of cases in 2005, hundreds of thousands in 2006) they were not different with respect to the efficacy of transmission as measured by the reproduction number. In other words, each case infected approximately the same number of secondary cases in the first and second waves of the epidemic. These results challenge that a change in virulence was necessary to obtain a large epidemic(Schuffenecker et al. 2006). Rather, the mere difference in the number of infected individuals at the start of the two waves (few versus few hundreds) combined with a reproduction number between 3 and 4 for Chikungunya fever were sufficient to explain this change in magnitude. The temporal profile in R shows that epidemic progression was first cut down first after July 2005, likely due to the decreased density of mosquitoes during (austral) winter. However, the reproduction number did not vanish, and 100 to 200 new cases kept appearing each week during the austral winter. As soon as mosquitoes appeared again, in December 2005, the epidemic was so well seeded that a dramatic and rapid increase in incidence was unavoidable.

The main source of uncertainty regarding estimation of the reproduction number came from our limited knowledge of the GI for Chikungunya fever. The method we proposed to determine the GI does not require knowledge of the vector's demographics, since it focuses on the human to human generation interval. Importantly, the human to human GI does not depend on how many bites per GC are possible, as long as this number remains the same with time, neither does it depend on the actual number of mosquitoes but rather on the age structure of the vector population in terms of GC. On the contrary, the number of mosquitoes involved in transmission will crucially depend on the hypothesized number of bites per GC.

We introduced the parameter ρ to weight down the importance of GCs with time since infection of the vector. One may interpret ρ as a constant mortality rate per GC for the vectors

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once they are infectious, that is provided they survived the first K_{MIN} cycles after becoming infected. Indeed, if there is a ρ=50% mortality rate per infectious GC, the importance of the first infectious GC will be twice as much as the second, and so on, as captured by the relative weights π_k used in the generation interval. A large ρ value will therefore lead to a short infectious lifespan. If the mortality rate of an infectious mosquito is not much superior to that of another insect, ρ may also correspond to the overall mortality rate per GC, with large values of ρ associated with a short lifespan of the vector, as is common in the field.(Anderson and May 1991)

To best show how the uncertainty on the GI led to changes in the R estimates, we used a wide range of plausible values and reported extreme cases. The real R profile likely lies in between these extreme cases. We found that increasing the average GI (either by increasing K_{MIN} or decreasing ρ) caused the reproduction number to increase. Indeed, secondary cases tended to put more weight on the less numerous earlier index cases with increasing average GI. As a consequence, the reproduction number increased. The opposite was observed when the epidemic curve was decreasing, with smaller R values associated with longer GIs. The posterior validation study showed that the estimates of R captured the essential features of the epidemic (Figure 5). It also showed that while estimates were readily obtained for any choice of the GI, some choices reproduced the epidemic dynamics better. For example, it was necessary to include a latent period of at least one GC so that the magnitude of surrogate epidemics matched the actual data. It is tempting to relate this latency to the few days that are necessary for the virus to be present in the salivary glands of the mosquito after infection (White 1987). Overall, the distance between surrogate epidemics and the actual data was the smallest for one GC latent period and a large value of ρ. A short infectious lifespan for the mosquito, almost limited to the first GC after latency, was enough to ensure the spread of the disease.

A second limitation arose from the change from individual case ascertainment to GP based extrapolation at the beginning of the second epidemic wave. The time of this change

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coincided with the largest weekly increase in incidence of the whole epidemic (+200% in one week), suggesting under reporting in the first wave and/or over estimation in the second. We examined the effect of under reporting on the estimate of R by adding up to 50% "unreported" cases in the first wave. There were no qualitative changes in the temporal profile of R. The peak in reproduction number during the second wave tended to decrease as the number of underreported cases grew (data not shown). Importantly, the results of a seroprevalence study on 2400 persons in Réunion Island after the second epidemic wave found 38% IgG positive (Perreau et al. 2007), in very good accordance with the cumulated attack rate of 34% from the epidemic curve.

Last, we did not consider changes in the GI due to seasonal changes in the GC length. Figure 3 and 4 already suggest that the estimates of R during winter were robust to the choice of the GI. To investigate this issue further, we estimated R with a time varying GI based on a 5 days GC during summer and a 10 days GC during winter (from mid-June to November). There was little effect on the overall profile and magnitude of the reproductive number, but increasing the GI duration during winter caused R to increase again earlier. Indeed, increasing the average GI duration from, say, 2 to 3 weeks makes cases infected 3 weeks before more likely to be index cases than cases infected 2 weeks before. As a consequence, secondary cases are imputed to index cases appearing earlier in time and R rises earlier. Independently from seasonal changes, the GI may have been shortened during the second season with increasing awareness and pest control. If all GIs had been reduced to less than one week, the proposed method would simplify to the much simpler ratio of weekly incidences. However, since at least 5% of the cases have an incubation period longer than 6 days, the GI distribution may not show such a reduction.

Several additional hypotheses were necessary concerning the epidemic. First, we considered that all infected cases were eventually symptomatic and reported. This is in accordance with textbooks,(Peters and Dalrymple 1990). Preliminary results from a seroprevalence study conducted in Réunion island show that less than 6% cases were

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asymptomatic. A second hypothesis was that cases were not imported during the course of the epidemic. While this assumption is probably not met, given Chikungunya is currently present in the whole region, our results should not be overly affected since the size of the epidemic must have kept the fraction of imported cases very small. We also required that human hosts constituted the main reservoir for the virus. Monkeys are known hosts of the virus(Inoue et al. 2003; McIntosh et al. 1963), but are not present on the island; and other animals do not seem to be common hosts of the virus(Adesina and Odelola 1991; Guilherme et al. 1996; McIntosh et al. 1963). Finally, we assumed that the mosquito was purely a vector, and excluded vertical or sexual transmission in mosquitoes since this is reportedly the case in Chikungunya fever(Mourya 1987; Zytoon et al. 1993).

The posterior validation study allowed comparing predicted incidences with actual incidences, providing a diagnostic check of how well the R profile and corresponding GI described the whole epidemic. The same data was used to estimate R and evaluate the fit, a practice that generally leads to reduce bias at the expense of increased variance in model selection (Hastie et al. 2001). In other words, while the selected GI led to the best fit for the Réunion Island epidemic, there is no guarantee that it would be the best choice for another Chikungunya fever epidemic. We also acknowledge that our analysis disregarded some factors (temperature, rain, season,…) which may be important for the actual GI duration in the field.

A strain of Chikungunya virus has been circulating in East Africa and the Indian Ocean region for a couple of years(Schuffenecker et al. 2006). Previous epidemics were little documented due to limited resources for surveillance, while real time surveillance was possible in Réunion Island. Yet, the disease could develop into a major public health problem leading to hundred thousands cases. This strongly suggests that progress in disease surveillance allowed by new information technologies must be matched by improvement in data analysis as proposed here. Indeed, early calculation of the initial reproduction number, which would have been possible after the first season, would have confirmed the potential for

major outbreaks. Indeed, the cumulated attack rate for the simple epidemic is greater than 1-1/R_0(Anderson and May 1991; Diekmann and Heesterbeek 2000).Taking the whole range of R_0 values, from 2 to 11, this meant that the cumulated attack rate could range from 50 to 90%. In the best fitting case (R_0=3.7), this rate would have been 73%, in good agreement with the 75% and 67% seen in Kenya and Comoros(Breiman et al. 2006). With more than 60% of the population still susceptible, the possibility of a renewed outbreak in Réunion Island may not be excluded as long as viral strains circulate in the region.

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References

Adesina, OA, Odelola, HA. Ecological distribution of Chikungunya haemagglutination inhibition antibodies in human and domestic animals in Nigeria. Trop Geogr Med 1991; 43: 271-275.

Anderson, RM, May, RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford Science Publications;1991.

Breiman, R, Sergon, K, Sang, R, Burke, H, et al. RAPID Re-emergence of Chikungunya Virus in East Africa. ICEID 2006, Atlanta, Georgia, USA: 2006.

Cauchemez, S, Boelle, PY, Donnelly, CA, Ferguson, NM, et al. Real-time estimates in early detection of SARS. Emerg Infect Dis 2006; 12: 110-113.

Diekmann, O, Heesterbeek, J. Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation. New York: Wiley & Sons;2000.

Fine, PE. The interval between successive cases of an infectious disease. Am J Epidemiol 2003; 158: 1039-1047.

Guilherme, JM, Gonella-Legall, C, Legall, F, Nakoume, E, et al. Seroprevalence of five arboviruses in Zebu cattle in the Central African Republic. Trans R Soc Trop Med Hyg 1996; 90: 31-33.

Hastie, T, Tibshirani, R, Friedman, J. The Elements of Statistical Learning. New York: Springer-Verlag;2001.

Inoue, S, Morita, K, Matias, RR, Tuplano, JV, et al. Distribution of three arbovirus antibodies among monkeys (Macaca fascicularis) in the Philippines. J Med Primatol 2003; 32: 89-94.

Laras, K, Sukri, NC, Larasati, RP, Bangs, MJ, et al. Tracking the re-emergence of epidemic chikungunya virus in Indonesia. Trans R Soc Trop Med Hyg 2005; 99: 128-141.

McIntosh, B, Paterson, H, Donaldson, J, de Sousa, J. Chikungunya virus: viral susceptibility and transmission studies with some vertebrates and mosquitoes. S Afr J Med Sci 1963; 28: 45-52.

Mori, A, Wada, Y. The gonotrophic cycle of *Aedes albopictus* in the field. Trop. Med. 1977; 19: 141-146.

Mourya, DT. Absence of transovarial transmission of Chikungunya virus in Aedes aegypti & Ae. albopictus mosquitoes. Indian J Med Res 1987; 85: 593-595.

Paquet, C, Quatresous, I, Solet, J, Sissoko, D, et al. Épidémiologie de l'infection par le virus Chikungunya à l'Ile de la Réunion: point de la situation au 8 janvier 2006. BEH 2006; 2-3.

Paquet, C, Quatresous, I, Solet, JL, Sissoko, D, et al. Chikungunya outbreak in Reunion: epidemiology and surveillance, 2005 to early January 2006. Euro Surveill 2006; 11: E060202 060203.

Perreau, J, Catteau, C, Michault, A, Parain, C, et al. Fin 2006, 300000 personnes avaient été atteintes par le Chikungunya [By the end of 2006, 300000 people had been infected with Chikungunya]. Economie de la Réunion 2007; 129: 16-17.(available at http://www.insee.fr/fr/insee_regions/reunion/prodser/pub_elec/revue/revue129/revue129_chikungunya.html)

Peters, C, Dalrymple, J. Alphaviruses. In: Fields, B, Knipe, D. Virology. New York: Raven Press Ltd. 1990:

Reiter, P, Fontenille, D, Paupy, C. Aedes albopictus as an epidemic vector of chikungunya virus: another emerging problem? Lancet Infect Dis 2006; 6: 463-464.

HAL author manuscript inserm-00167421, version 1

Roberts, MG, Heesterbeek, JA. A new method for estimating the effort required to control an infectious disease. Proc Biol Sci 2003; 270: 1359-1364.
Ross, RW. The Newala epidemic. III. The virus: isolation, pathogenic properties and relationship to the epidemic. J Hyg (Lond) 1956; 54: 177-191.
Schuffenecker, I, Iteman, I, Michault, A, Murri, S, et al. Genome Microevolution of Chikungunya Viruses Causing the Indian Ocean Outbreak. PLoS Med 2006; 3: e263.
Wallinga, J, Teunis, P. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am J Epidemiol 2004; 160: 509-516.
White, G. Mosquitoes. In: Manson-Bahr, P, Bell, D. Manson's tropical diseases. London: Baillière Tindall. 1987:
Zytoon, EM, el-Belbasi, HI, Matsumura, T. Transovarial transmission of chikungunya virus by Aedes albopictus mosquitoes ingesting microfilariae of Dirofilaria immitis under laboratory conditions. Microbiol Immunol 1993; 37: 419-421.

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APPENDIX:

1 – INCIDENCE EXTRAPOLATION

Starting in December 2005, the cases were not individually ascertained as before. The incidence of Chikungunya fever was therefore calculated from a sentinel network of 31 GPs in Réunion Island using sampling formulas. First, a sampling weight w_i was determined for each GP as the ratio of the number of cases they had reported during the first epidemic (to the end of May 2005) to the overall epidemic size. Second, the incidence in week t, n_t was extrapolated from the number of cases $c_{t,i}$ reported by the i-th of the N participating GPs in the week t according to the formula: $n_t = \frac{1}{N}\sum_i \frac{c_{t,i}}{w_i}$

2 - GENERATION INTERVAL

One realisation $t^{(k)}$ of the GI corresponding to bites k GC apart is obtained as follows:

1) T_V : The date of symptoms occurrence relative to the first day of positive viremia is sampled form (1, 2) days with probability (2/3, 1/3) for the index case
2) T_B : The date of mosquito bite is sampled uniformly from 0 to 6 days following the first day of viremia
3) T_M : The date of the k-th blood meal is obtained by summing k independent realizations of the GC length (uniform on 4, 5, 6 days)
4) T_I : The dates of symptoms after a bite are sampled from a lognormal distribution with mean 3 and standard deviation 1.3.

The realization is therefore $t^{(k)} = -t_V + t_B + t_M + t_I$.

For each value of k, we repeated this algorithm 100,000 times, and estimated the probability function $f^{(k)}(d)$ that the GI is d days in case of bites k GC apart by

$$f^{(k)}(d) = \frac{1}{100000}\sum_i 1\{t_i^{(k)} = d\}.$$

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An estimate of the GI for chosen values of ρ and K_{MIN}, was finally $f(d) = \sum_{k>K_{MIN}} \pi_k f^{(k)}(d)$ for a duration *d* between symptoms. These probabilities were aggregated by weeks to compute the w(j).

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FIGURE LEGENDS

Figure 1 : Framework for the determination of the generation interval.

Figure 2: Distribution of the generation interval according to relative weight of successive gonotrophic cycles and latent period. (left) short infectious lifespan (ρ=1), (right) long infectious lifespan (ρ=0). In both panels, latency: 0 cycle (dotted, K_{MIN}=1), 1 cycle (plain, K_{MIN}=2), 2 cycles (dashed, K_{MIN}=3). (PDF : probability density function.)

Figure 3 : Epidemic curve and reproduction number during the Chikungunya fever epidemic, La Réunion. (Top) epidemic curve for the two consecutive waves (logarithmic scale). Estimates of the reproduction number R according to mosquito infectious lifespan and latent period (middle: short infectious lifespan ρ=1, bottom ρ=0; in both panels latency: 0 cycle (dotted, K_{MIN}=1), 1 cycle (plain, K_{MIN}=2), 2 cycles (dashed, K_{MIN}=3).

Figure 4: Weekly reproduction number during the two epidemic waves in Réunion Island according to mosquito mortality rate during the infectious period. The reproduction number was estimated in the case of 1 cycle latency (K_{MIN}=2).

Figure 5: Observed and averaged simulated epidemic according to relative weight of successive gonotrophic cycles and latency in the mosquito. (left) short infectious lifespan (ρ=1); (right) long infectious lifespan (ρ=0). In both panels: no latency (dotted), 1 cycle latency (plain), 2 cycles latency (dashed). Dots show the observed incidence during the first epidemic wave.

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Table 1: Notations, definitions and symbols

Symbol	Definition (*commentaries*)	Values	Unit	Ref.
GC	Gonotrophic cycle: the process of blood-feeding, egg maturation and oviposition[laying eggs] in the female mosquito. (White 1987)	Uniform distribution on 4, 5, 6 days	days	(Mori and Wada 1977)
GI	Generation interval : the interval between symptom onset in one index case and symptom onset in his secondary cases(Fine 2003).	from T_V, T_B, T_M, T_I, ρ and K_{MIN}	week	
$\mathbf{T_V}$	Time from infectiousness to symptoms in the human host. *(Coincides with detectable viremia before symptom onset)*	1 day (probability 2/3) or 2 days (probability 1/3)	days	(Peters and Dalrymple 1990)
$\mathbf{T_B}$	Time from infectiousness in an infected human host to a mosquito bite. *(Occurring any time during detectable viremia in the human host)*	Uniform distribution on 1 to 7 days	days	(Peters and Dalrymple 1990)
$\mathbf{T_M}$	Time from initial contaminating bite to a transmitting bite in a mosquito. *(It is a multiple of the duration of the gonotrophic cycle)*	Distribution on 5 [4-6]days, 10 [8-12]days,…	days	*see GC*
$\mathbf{T_I}$	Time from infection to symptoms in the human host. *(Generally 2-3 days, but may be longer)*	Lognormal (mean 3 standard deviation 1.3)	days	(Peters and Dalrymple 1990)
ρ	Mosquito mortality rate by gonotrophic cycle once infectious. *(allows weighing the importance of GCs following contamination for transmission)*	Between 0 and 1	prob.	
$\mathbf{K_{MIN}}$	Number of GC after contamination before a mosquito may transmit the disease. *(1 means that the mosquito transmits during the GC following contamination)*	1,2, 3 or 4	GC	
π_k	Relative weight in transmission of the *k*-th GC following contamination *(We limited transmission to the first 8 GC following contamination)*	$\pi_k \propto (1-\rho)^{k-1}$, $1 \leq k \leq 8$	prob.	
$\mathbf{w_j}$	Probability distribution function for the generation interval. *(Percentage of secondary cases occurring j weeks after the index case)*	from T_V, T_B, T_M, T_I, ρ and K_{MIN}	prob.	*see GI*
$\mathbf{n_t}$	Disease incidence in week *t*	Local health authorities		www.invs.sante.fr
$\mathbf{R_t}$	Reproduction number of the disease. (Wallinga and Teunis 2004) *(Average number of secondary cases for a case infected at date t)*	To be estimated	persons	
$\mathbf{R_0}$	Initial reproduction number. (Anderson and May 1991) *(Number of secondary cases for the first case in a wholly susceptible population)*	To be estimated	persons	

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Table 2: Distance between observed and average simulated epidemic, according to mosquito lifespan (ρ) and latency period (K_{MIN}).

		K_{MIN}			
		1	2	3	4
ρ	0	1744	434	332	338
	0.25	2022	266	278	366
	0.5	2352	137	232	410
	0.75	3188	72	156	351
	1.0	3773	44	94	316

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FIGURE 1

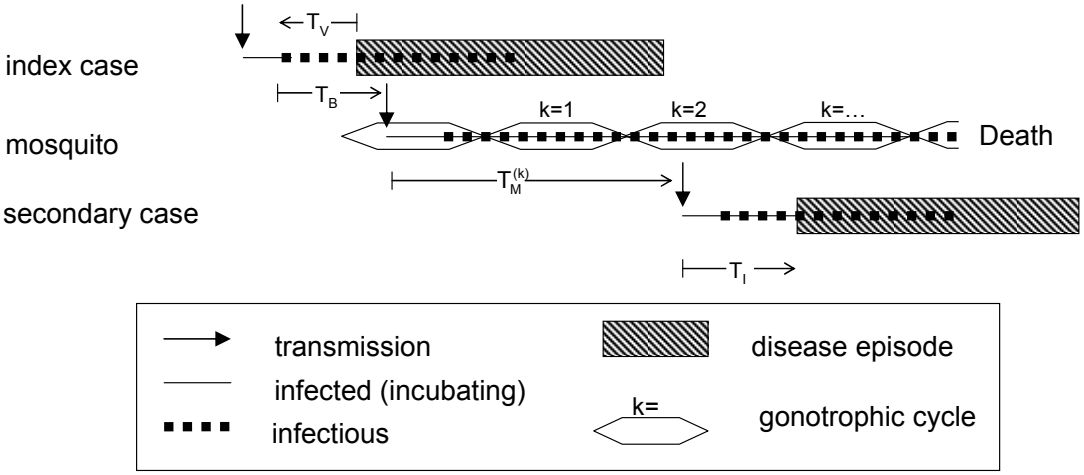

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FIGURE 2

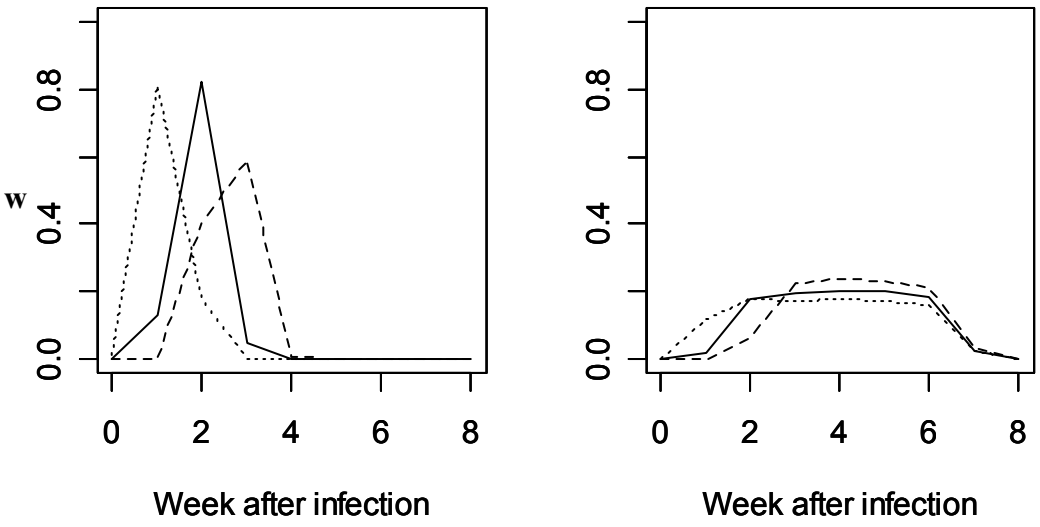

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FIGURE 3

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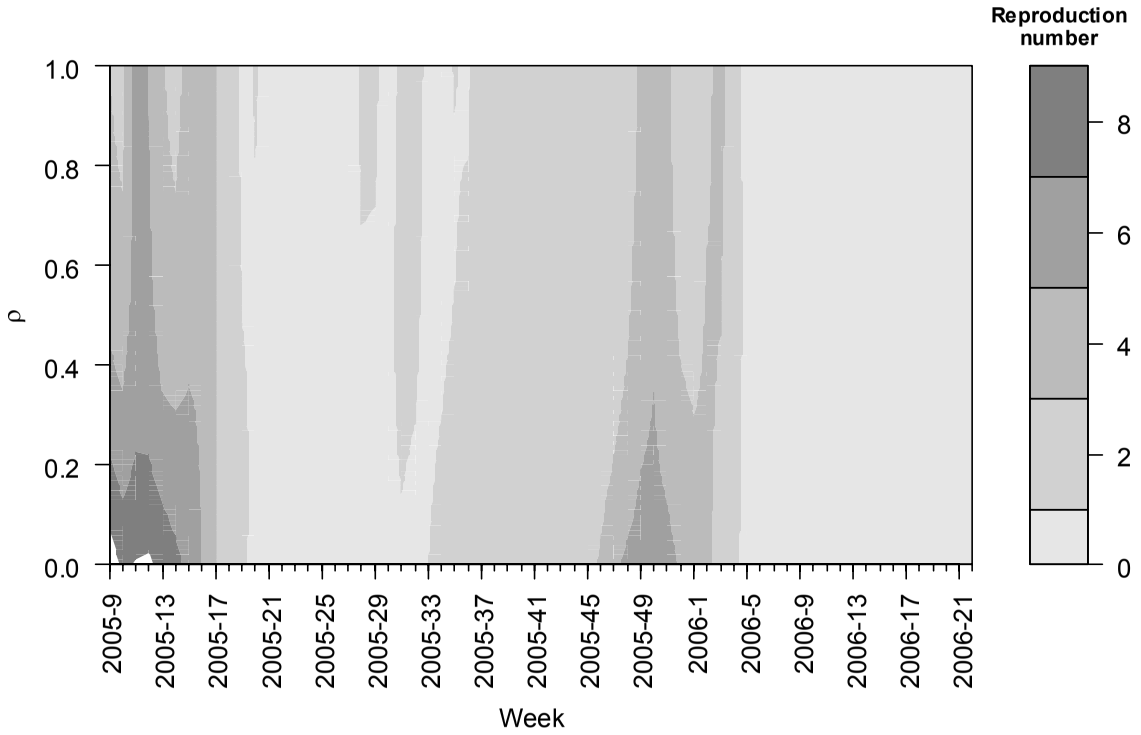
FIGURE 4



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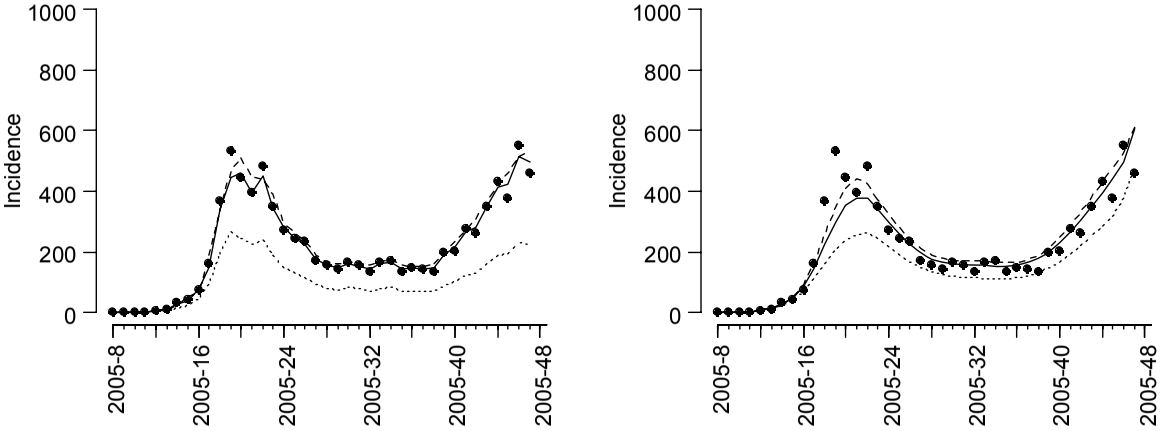
FIGURE 5