MEETING REPORT

Expert meeting on chikungunya modelling

Stockholm, April 2008

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Table of contents

Content iii
Summary: Research needs and data access 1
Introduction 2
Background 3
Meeting objectives 3
Presentations 4
Jolyon Medlock: Understanding environmental determinants for the establishment and spread of *Aedes albopictus* 4
Francis Schaffner: Entomological aspects related to chikungunya modelling for Europe — the bionomics of *Aedes albopictus* 7
Asghar Talbalaghi: Intervention and vector control 12
Pierre-Yves Boelle: Investigating a two-wave chikungunya fever epidemic in Réunion Island, 2005–06 13
Andrea Pugliese: Modelling approaches in Italy 17
Nicolas Bacaer: The basic reproduction number for vector-borne diseases with a periodic vector population 22
Conclusion 27
Participants 28
References 29
Agenda 30

Summary: Research needs and data access

During the course of the expert meeting, entomologists and modelling experts identified the following areas in need of research funding. Additional funding is needed to:

- interpret the effects of interventions;
- measure the sampling bias associated with mosquito traps in order to assess the actual size of a mosquito population;
- develop standardised methods in order to measure mosquito activity during an outbreak;
- develop mathematical models which can incorporate mosquito activity as an additional component; and to
- develop methods of how to quantify the risk of mosquito importation and establishment in areas where mosquitoes have not been previously present. (ECDC is already funding one project in this area.)

All proposed measures are aimed at improving modelling activities that can help to predict chikungunya outbreaks.

Data for modelling have to be accurate, accessible, and in the required format. During the outbreaks in Réunion (see page 20), data accessibility was rather spotty. This applies both to data accessibility within Réunion and the data flow between Réunion and other countries. In addition to ensuring that data are accessible, it is important to specify the exact data type that is used for reporting. The data reported from Réunion in 2006 were interpolated data from visits by general practitioners.

Introduction

Following recent outbreaks of chikungunya in Réunion and Italy — the latter outbreak being the first instance of local transmission in continental Europe — it became clear that there is a need for epidemiological models that can be used to predict future outbreaks and at the same time inform public health institutes of impending outbreaks. Some activity is already underway in this area, but research is hampered by insufficient access to data. Also, the research community needs to address methodological approaches and knowledge gaps. Additional research on how outbreak modelling can be used to measure the effects of public health interventions is also required.

ECDC organised the April 2008 'Expert meeting on chikungunya modelling' in order to facilitate the discussion between modellers and other experts on chikungunya.

In January 2008, leading chikungunya modellers held a teleconference during which it was agreed to organise an expert meeting on chikungunya modelling in order to ensure the exchange of experience on mathematical modelling between experts in chikungunya-affected countries and experts from fields related to vector-borne diseases such as entomology.

The aim of the expert meeting in April 2008 was to identify areas for further research at the European level. This meeting report is distributed to external stakeholders and funding agencies in order to inform them about the current state of disease modelling.

ECDC activities in this area included an expert consultation on chikungunya risk assessment for Europe (Stockholm, March 2006); on-site visits to the Italian regions affected by chikungunya in 2007; an expert consultation on vector-related risk for Chikungunya virus (CHIKV) transmission in Europe (Paris, October 2007); research aimed at assessing the magnitude and importance of vector-borne diseases in Europe; and a vector risk mapping initiative.

Background

Mathematical modelling of chikungunya started [1] with a computer simulation approach. Some of the more recent papers have focused on different methods for calculating the basic reproduction number R_0 within a periodic vector population [2]. Most modelling papers focus on the vector, but there is a noticeable lack of research as far as the inclusion of humans into the mathematical models is concerned. Most of the work in this area is being done in France and Italy, which use different approaches in their calculations [ECDC teleconference, January 2008].

With respect to modelling methods, a vast number of contentious issues exist. Most studies, published and unpublished, have found the value of R_0 to be about 3–4. In order to eliminate an outbreak, R_0 should be reduced to less than one. One approach is to monitor its value in real time which is particularly helpful when observing the effects of interventions. When mathematically modelling disease outbreaks, a variety of disciplines are involved, ranging from the obvious (mathematics) to entomology and decision making (both for public health and interventions). One problem frequently encountered with R_0 is that the same dataset can yield different R_0 estimates when different methods are used. This issue needs more attention, both inside and outside the modelling community.

The Stockholm meeting in April 2008 had a clear focus on modelling, but in order to get a better look at the knowledge gaps in the area, scientist in related fields were also invited, thus ensuring that their expertise could be incorporated into the existing modelling methods.

Meeting objectives

In order to discuss how modelling can be used to measure the effects of interventions during an outbreak and estimate the risk of chikungunya establishment in EU Member States, the meeting participants had to:

- map and assess different modelling approaches to chikungunya;
- agree upon key epidemiological parameters and model structures for modelling chikungunya outbreaks in Europe;
- ensure that entomological knowledge was incorporated into the modelling approaches; and
- discuss which kind of data is to be collected from future outbreaks and how it will be shared with modellers.

The second objective was to identify knowledge gaps in areas that require more research.

Presentations

Jolyon Medlock: Understanding environmental determinants for the establishment and spread of *Aedes albopictus*

The presentation focused on:

- work ongoing in the ECDC TigerMaps project; and
- published work by the British Health Protection Agency (HPA), funded by a grant-in-aid from the British government.

The key question currently addressed in the United Kingdom is if *Aedes albopictus* can be imported and if it can become established in the British climate. If the mosquito can be established, can it be active for a sufficient period of the year to cause a biting nuisance? The United Kingdom is one of the biggest importers of used tyres, which is a major factor for the spread of *Aedes albopictus* in the EU. Major import points are London and the port cities.

A study is underway to determine the northernmost latitude limit of *Aedes albopictus* and thus evaluate the establishment risk for the United Kingdom. A major risk factor is the importation of temperate strains.

Tropical populations are active year around. Temperate strains are seasonally affected by daylight, able to withstand low winter temperatures, thus permitting egg diapause. According to [3], the 'northerly limit of survival is considered to be influenced by a combination of photoperiod, temperature, humidity, and quantity/frequency of precipitation'.

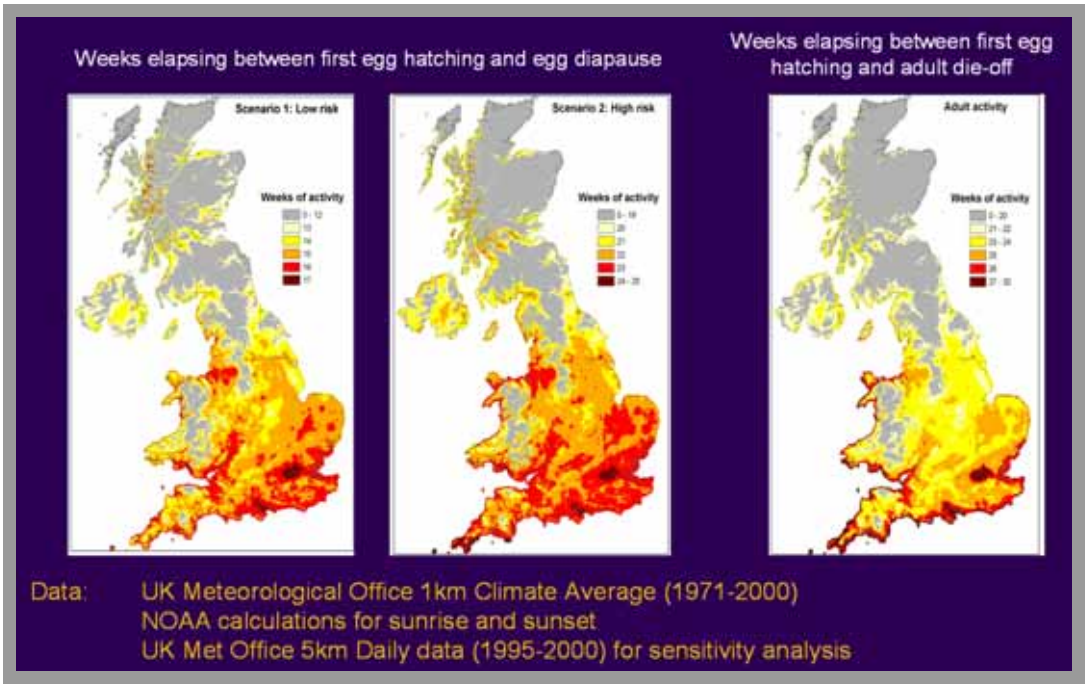
Winter temperature (mean January isotherm) thresholds are considered to be -3 ºC in China (January isotherm, mean) and between 0 ºC and -2 ºC in Japan, with 0 ºC as the tolerance limit for over-wintering in North America. This was confirmed by CDC maps on the spread of *Aedes albopictus*. Burgess [4], along with other studies, sees the over-wintering threshold at 0 ºC, which is generally accepted as the threshold for Europe.

Another important factor is the annual mean rainfall. Sufficient rain ensures that the aquatic breeding sites are filled. 500 mm per annum seems sufficient to fill appropriate aquatic sites [3, 5-8]. Lower annual rainfall is a limiting factor, particularly in southern Europe. However, precipitation must be relatively frequent during summer in order to provide the mosquito with breeding sites.

In summary, there are three main factors: winter temperature (permitting winter egg survival), annual rainfall (sufficient to fill aquatic breeding sites), and summer rainfall (to sufficiently maintain immature production).

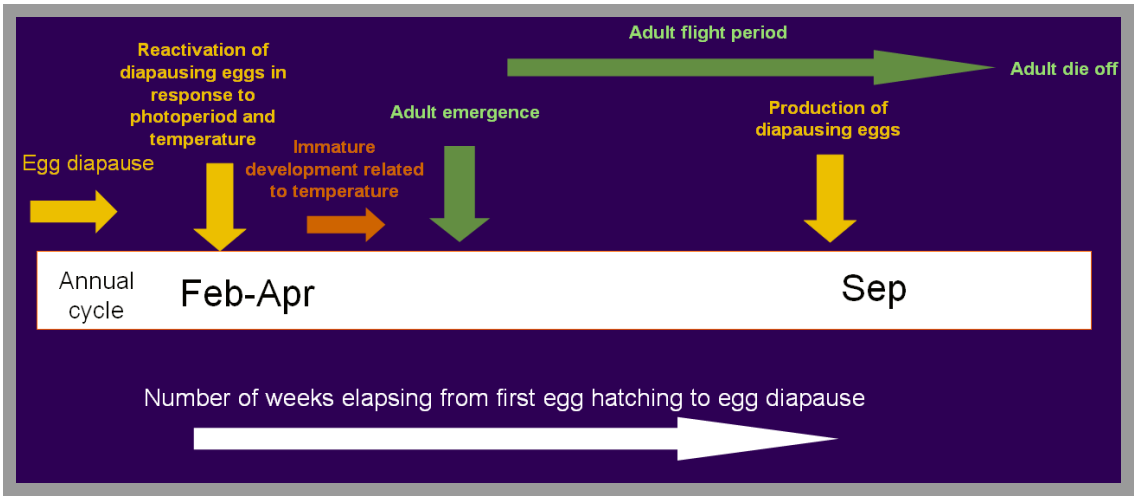
Medlock also developed a model that captured the mosquito's life cycle. Mean weekly temperatures and weekly photoperiod data were used to predict the week of egg emergence in spring, and the week of egg diapause and adult die-off in autumn (see Figure 1). While this approach cannot predict abundance, it serves as a decent substitute.

Figure 1. Weeks elapsing between first egg hatching and egg diapause / adult die-off



A look at the annual cycle shows that 16–24 weeks are likely to elapse between egg hatching and egg diapause across southern England, with up to 32 weeks of adult activity. However, eggs required to survive more than six months could desiccate at low temperature/humidity. For more details of key input parameters please refer to Figure 2.

Figure 2. Egg survival, key input parameters



Studies in Japan [9] have shown that average temperatures above 11 ºC supported *Aedes albopictus* populations, and temperatures above 12 ºC supported a more stable establishment: the population remained above the threshold for 186 days. These temperature data are also good indicators for populations in the US. The biological significance is unclear, as mean values do not capture the effects of very high summer and very low winter temperatures.

Main environmental determinants are:

- winter temperatures (winter egg survival);
- annual rainfall (sufficient to fill aquatic breeding sites);
- summer rainfall (immature production); and
- summer temperatures (promote speed of development of immature insects, speed of gonotrophic cycles, and hence increased abundance).

The TigerMaps project, funded by ECDC, has two main goals: to collect better field data and provide better maps. TigerMaps wants to assess the combined risk level for *Aedes albopictus* establishment in Europe by using recent climatic datasets and monthly time-series of eco-climate data covering the last five years. Included factors are temperature, rainfall, vegetation activity, evapotranspiration and other spatial data. One outcome will be the prediction of shifts in mosquito establishment caused by changes in temperature and rainfall.

Questions and comments

Tyre-importing sites in the United Kingdom are difficult to monitor because of limited funds and the lack of approval to monitor these sites. Plans exist to learn from France's experience when identifying relevant sites of importation. Identifying the companies that import used tyres is still a work in progress.

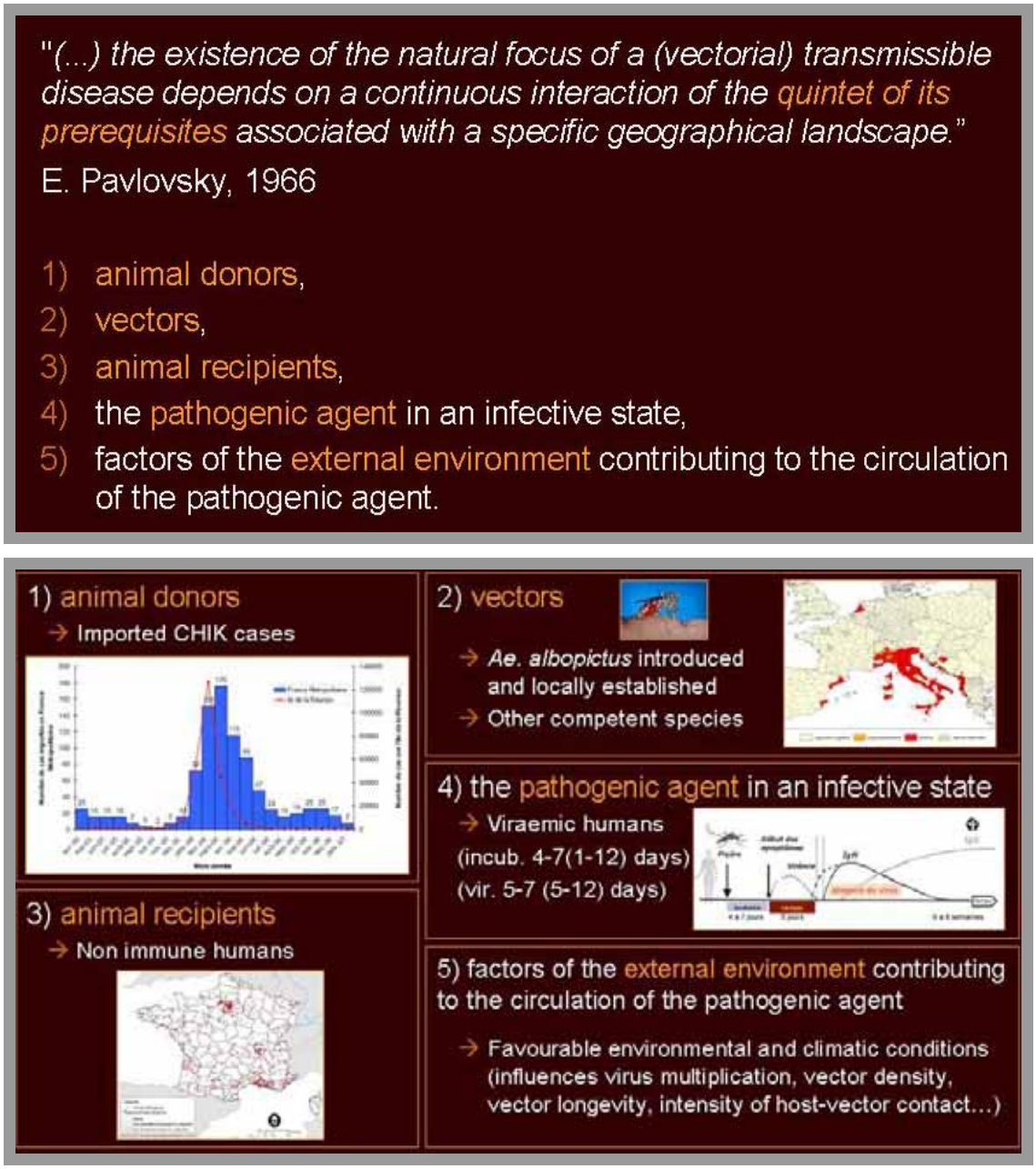
The human population density is also important. A multivariate approach is needed, where temperature and rainfall may be correlated.

Pathways of introduction need to be identified, e.g. 'lucky bamboo' or imported tyres (ports, highways). About 250 companies in France import tyres. One possible step is the production of risk maps that show the location of tyre importers and traffic routes connecting to them.

It also needs to be established how *Aedes albopictus* is transported within Europe, since it can be found in Germany, north of the Alps. One approach is to trace DNA through microsatellites in mosquito populations (in collaboration with the Directorate-General for Research/Directorate-General for Health and Consumers). Ideal for research are newly established populations that can be traced to their origin. Parallels could be drawn to similar studies on *Aedes japanicus* in Japan, France and Belgium. A current research project in Sweden is using microsatellites but is limited to two species.

Francis Schaffner: Entomological aspects related to chikungunya modelling for Europe — the bionomics of *Aedes albopictus*

Figure 3. **Chikungunya fever and its dependence on the continuous interaction of five factors**



Introduction risk:

- Several European countries have reported imported cases
- 300 000 French tourists visited Réunion
- 9 April 2005–31 May 2006: 635 imported cases in metropolitan France
- Viraemic hosts (5–7 days)

Transmission risk:

- Increased risk in areas where a potential vector proliferates:
  - need for data on *Aedes albopictus* distribution;
  - need for data on vector competence of local mosquitoes.
- Increased risk if vector capacity is high (related to competence but also host preference, density, longevity, etc.).
- Increased risk if climatic conditions are favourable (extrinsic cycle duration: virus present in salivary glands two days after infection).

Hosts are only non-immune humans. Donors are imported chikungunya cases, viraemic for 2–4 days. Comparable to dengue, the observed incubation period might not coincide with the latent period.

The external environment is contributing to the circulation of the pathogenic agent.

There is a risk of importation through tourism, particularly travellers visiting friends and relatives.

A PowerPoint slide presented at the expert meeting illustrated sylvatic chikungunya cycles in West Africa, based on research by Didier Fontenille at the Institut de recherche pour le développement, Montpellier, France.

A transmission risk exists where vector competent mosquitoes are present and find favourable climatic conditions. Figure 4 shows a detailed list of potential vectors.

Figure 4. Vectors of *Chikungunya virus*

2. Vectors of CHIKV

Genus ***Aedes***

- Subgenus ***Aedimorphus***: *Ae. dalzieli* (Africa)
- Subgenus ***Diceromyia***: *Ae. furcifer, Ae. taylori* (Africa)
- Subgenus ***Stegomyia***: *Ae. aegypti, Ae. africanus, Ae. luteocephalus* (Africa); *Ae. aegypti, Ae. albopictus* (Asia)

Espèce	Vecteur reconnu	Infection dans la nature	Transmission et Infection expérimentale	Pays de l'observation
MOUSTIQUES				
Aedes (Aedimorphus) abnormalis group		x		Côte d'Ivoire
Aedes (Aedimorphus) argenteopunctatus		x		Côte d'Ivoire, Sénégal
Aedes (Aedimorphus) cumminsii		x		Côte d'Ivoire
Aedes (Aedimorphus) dalzieli		x		Sénégal
Aedes (Aedimorphus) mutilus group		x		Côte d'Ivoire
Aedes (Diceromyia) cordellieri		x		Côte d'Ivoire
Aedes (Diceromyia) furcifer	x	x	x	Burkina Faso, Côte d'Ivoire, Mali, Sénégal
Aedes (Diceromyia) furcifer mâles		(x)		Côte d'Ivoire
Aedes (Diceromyia) furcifer-taylori	(x)	(x)	x	Afrique du Sud, Sénégal, S. Rhodesie
Aedes (Diceromyia) taylori	x	x		Nigeria, Sénégal
Aedes (Finlaya) ingrami		x		Côte d'Ivoire
Aedes (Finlaya) togoi			x	
Aedes (Fredwardsius) vittatus		x	x	Côte d'Ivoire, RCA, Sénégal
Aedes (Muricidus) grahami		x		Côte d'Ivoire
Aedes (Neomelaniconion) circumluteolus			négative	
Aedes (Neomelaniconion) jamoti		x		Côte d'Ivoire
Aedes (Neomelaniconion) palpalis group		x		Côte d'Ivoire
Aedes (Neomelaniconion) taeniorostris		x		Côte d'Ivoire
Aedes (Stegomyia) metallicus			x	
Aedes (Stegomyia) simpsoni			négative	
Aedes (Stegomyia) aegypti	x	x		Angola, Côte d'Ivoire, Nigeria, Sénégal, S. Rhodesie, Tanzanie, Thaïlande
Aedes (Stegomyia) africanus	x	x		Burkina Faso, Côte d'Ivoire, Ouganda, RCA, Sénégal, S. Rhodesie
Aedes (Stegomyia) africanus group		x		RCA
Aedes (Stegomyia) albopictus	x	x	x	Inde, Thaïlande
Aedes (Stegomyia) apicoargenteus			x	
Aedes (Stegomyia) ledgeri			x	
Aedes (Stegomyia) luteocephalus	x	x		Burkina Faso, Côte d'Ivoire,

Espèce	Vecteur reconnu	Infection dans la nature	Transmission et Infection expérimentale	Pays de l'observation
MOUSTIQUES (suite)				
Aedes (Stegomyia) neoafricanus		x		Sénégal
Aedes (Stegomyia) ochi		x		Côte d'Ivoire, RCA
Aedes (Stegomyia) usambara		x		Côte d'Ivoire
Aedes (Zavortinkius) fulgens			x	
Anopheles (Anopheles) coustani		x		Sénégal
Anopheles (Cellia) funestus		x		Côte d'Ivoire , RCA
Anopheles (Cellia) gambiae sp.A			négative	S. Rhodesie
Anopheles (Cellia) nili		x		Côte d'Ivoire
Anopheles (Cellia) rufipes		x		Sénégal
Anopheles (Cellia) stephensi			x	Inde
Coquillettidia (Coquillettidia) maculipennis		x		Côte d'Ivoire
Culex (Culex) decens group		x		Côte d'Ivoire
Culex (Culex) ethiopicus		x		Sénégal
Culex (Culex) quiarti		x		Côte d'Ivoire
Culex (Culex) pipiens (molestus)			négative	
Culex (Culex) poicilipes			négative	
Culex (Culex) quinquefasciatus		x	négative	Côte d'Ivoire, Tanzanie, Thaïlande
Culex (Culex) univittatus			négative	
Culex (Culex) weschei		x		Côte d'Ivoire
Culex (Culiolomyia) cinereus		x		Côte d'Ivoire
Eretmapodites chrysogaster			x	
Eretmapodites inornatus group		x		Côte d'Ivoire
Mansonia (Mansonioides) africana	?	x	x	Côte d'Ivoire, Nigeria, RCA
Mansonia (Mansonioides) uniformis		x		Côte d'Ivoire
Mansonia sp.		x		Ouganda
	6	31	12	
AUTRES INSECTES				
Tique - Alectorobius sonrai		1	négative	Sénégal
Tique - Ornithodos savignyi		1	négative	
Blatte		1		RCA
Punaise de lit - Cimex hemipotera		1		Tanzanie
		4	2	

A broad range of other mosquitoes in Africa can act as efficient vectors for chikungunya: *Aedes dalzieli*, *Aedes furcifer*, *Aedes taylori*, *Aedes aegypti*, *Aedes africanus*, and *Aedes luteocephalus*. For others, transmission efficiency or competence is not precisely known.

Expansion successes include larvae/adults that were transported with cargo (1850–1950). Currently, eggs are disseminated worldwide through the 'lucky bamboo' trade and used tyres. Adult mosquitoes are transported locally by ground vehicles from site to site.

A map by Scholte and Schaffner, presented during the expert meeting, showed the spread of the vector in Europe from 1979 (Albania) up until 2007 (Germany).

Aedes albopictus is a competent vector for 24 arboviruses.

Some arboviruses and parasites have been isolated from wild females:

- Dengue 1, 2, 3 and 4
- Chikungunya
- Japanese encephalitis
- West Nile
- La Crosse
- Cache Valley
- Dirofilaria

Aedes albopictus can experimentally transmit:

- chikungunya fever;
- Rift Valley fever;
- West Nile fever;
- yellow fever; and
- Tahyna.

Vector competence depends on the population and the virus. Vertical transmission for Chikungunya virus has recently been demonstrated.

Susceptibility varies between species. Among species, it varies between strains. A study on a population of *Aedes albopictus* established in the Alpes-Maritimes showed an infection rate of 77.1 % for Chikungunya virus. Other studies have shown ranges between 25 % and 48 %.

Data from Réunion and Mayotte show marked differences in infection rates. A graph based on data by Vazeille et al. (http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2064959) was used to illustrate the infection rates of *Aedes albopictus* from La Réunion and Mayotte to two CHIKV isolates: 05.115 (June 2005), 06.21 (November 2005).

Aedes albopictus is a competent vector for a high number of viruses, as confirmed by laboratory tests. With regard to bionomics, several factors affect vector capability, including egg survival, hatching, adult behaviour, and population dynamics.

In Europe, the mosquito mostly breeds in sites that are artificial, such as puddles in tyres lying outdoors and containers.

In the tropics, *Aedes albopictus* eggs have a low natural mortality (about 10 %) and a maximum longevity of 243 days. About 95 % of all eggs hatch after two months.

Survival for eggs in temperate areas during winter is several months. No information on summer egg mortality is available. During the expert meeting, the ability of *Aedes albopictus to* adapt to different climates was illustrated by a graphed based on the following research paper: Romi R, Severini F, Toma L. Cold acclimation and overwintering of female *Aedes albopictus* in Roma. J Am Mosq Control Assoc 2006;22:149–151.

All populations are likely to show some autogenous egg production, which ranges from 2.0 to 3.4 eggs/adult female.

The average lifetime fecundity varies between 300 and 345 eggs (42 to 88 eggs for the first egg batch).

Eggs from a single gonotrophic cycle can be laid in more than one oviposition site.

Mating:

- Between 48 and 72 hours after emergence
- A single male can inseminate six to seven females during its lifetime
- Females show no preference between males from different populations
- Males are attracted by hosts and attempt to mate females, outdoors and indoors; mating swarms occur
- Peak of activity in the morning and late afternoon
- Temperature of development: best between 25–30 ºC
- Longevity: several weeks

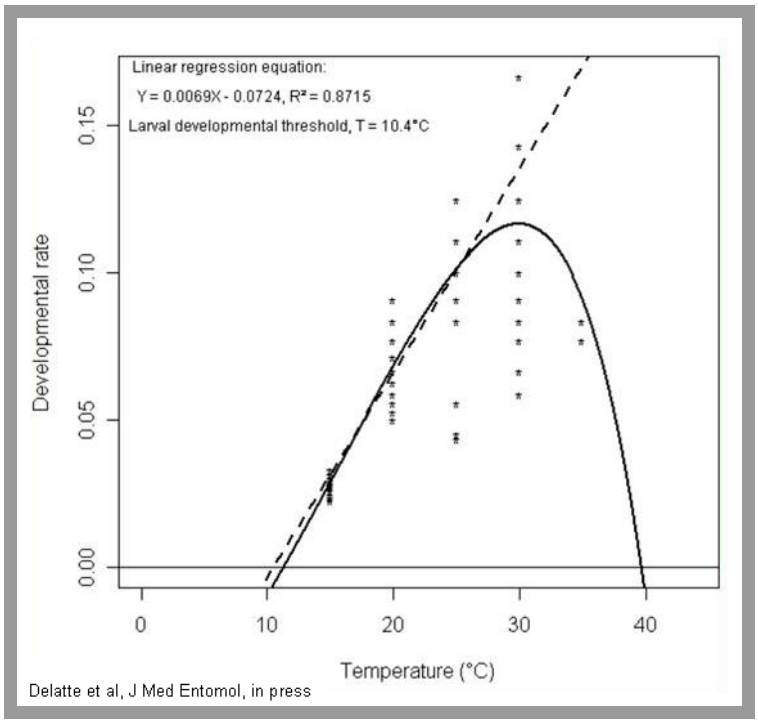
The larval development rate and its dependence on temperature are illustrated in Figure 5. The survival rate of females is shown in Figure 6.

Adults fly close to the ground, but not in strong winds. There is no wind-aided dispersal. Experiments with marked recaptured adults yield the following results:

- Maximum distance covered: 434 meters
- Mean distance after 10 days: 104 meters
- Probability of dispersal is greater for females from high-density larval rearing

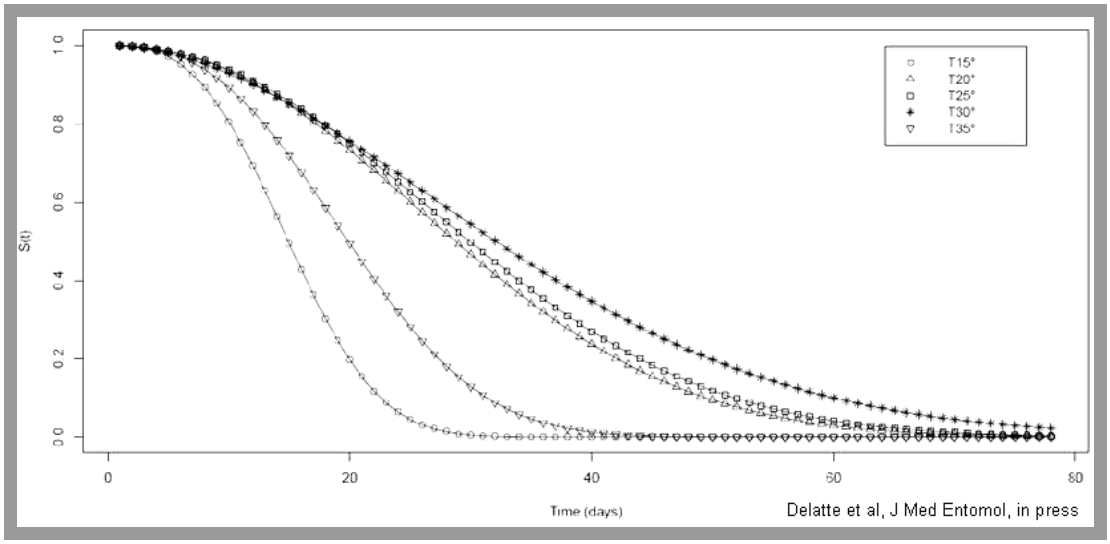
Adults could disperse as far as 200 meters, even if open space had to be traversed.

Figure 5. Temperature and larval development rate



Source: Delatte H, Gimonneau G, Triboire A, Fontenille D. Influence of temperature on immature development, survival, longevity, fecundity, and gonotrophic cycles of Aedes albopictus*, vector of chikungunya and dengue in the Indian Ocean. J Med Entomol. 2009 Jan;46(1):33-41.*

Figure 6. Survival rate of female *Aedes albopictus* mosquitoes



Source: Delatte H, Gimonneau G, Triboire A, Fontenille D. Influence of temperature on immature development, survival, longevity, fecundity, and gonotrophic cycles of Aedes albopictus*, vector of chikungunya and dengue in the Indian Ocean. J Med Entomol. 2009 Jan;46(1):33-41.*

The population size is closely related to the amount of rainfall.

Studies from Thailand show the presence of *Aedes albopictus* in tree holes. The mosquito can be active within a radius of 2 km.

The mosquito has a generation time of 3–8 weeks, producing 5–17 generations per year. Six different types of breeding sites exist.

Seasonal abundance:

- In tropical areas: all year, but abundance is much higher in summer
- In temperate areas: winter diapause induced by photoperiod (females exposed to 13–14 hours of daylight); high abundance in summer and autumn

During the Italian outbreaks over the last few years, three different routes of entry and dispersal were documented, see Figure 7. Figure 8 shows the seasonal dynamics of Italian populations of *Aedes albopictus.*

Figure 7. *Aedes albopictus*: routes of entry and dispersal

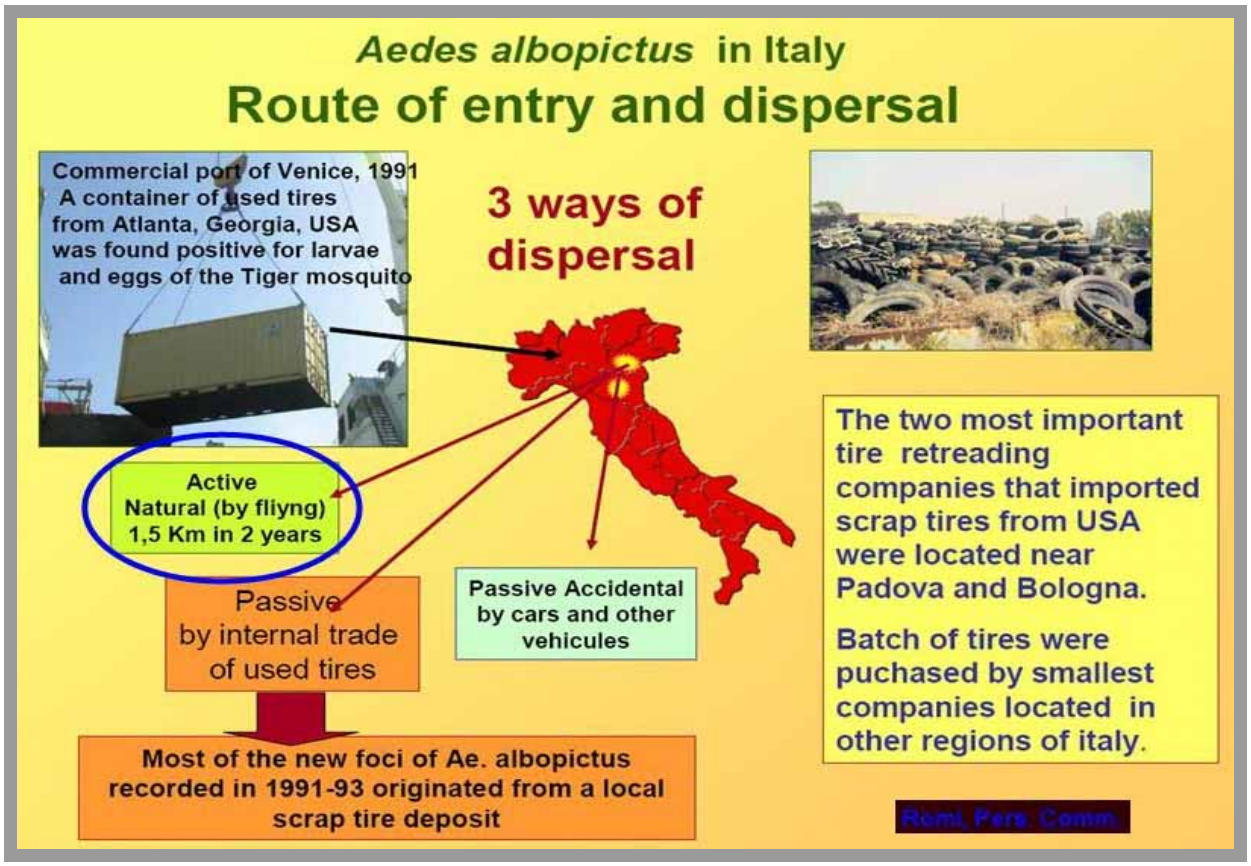
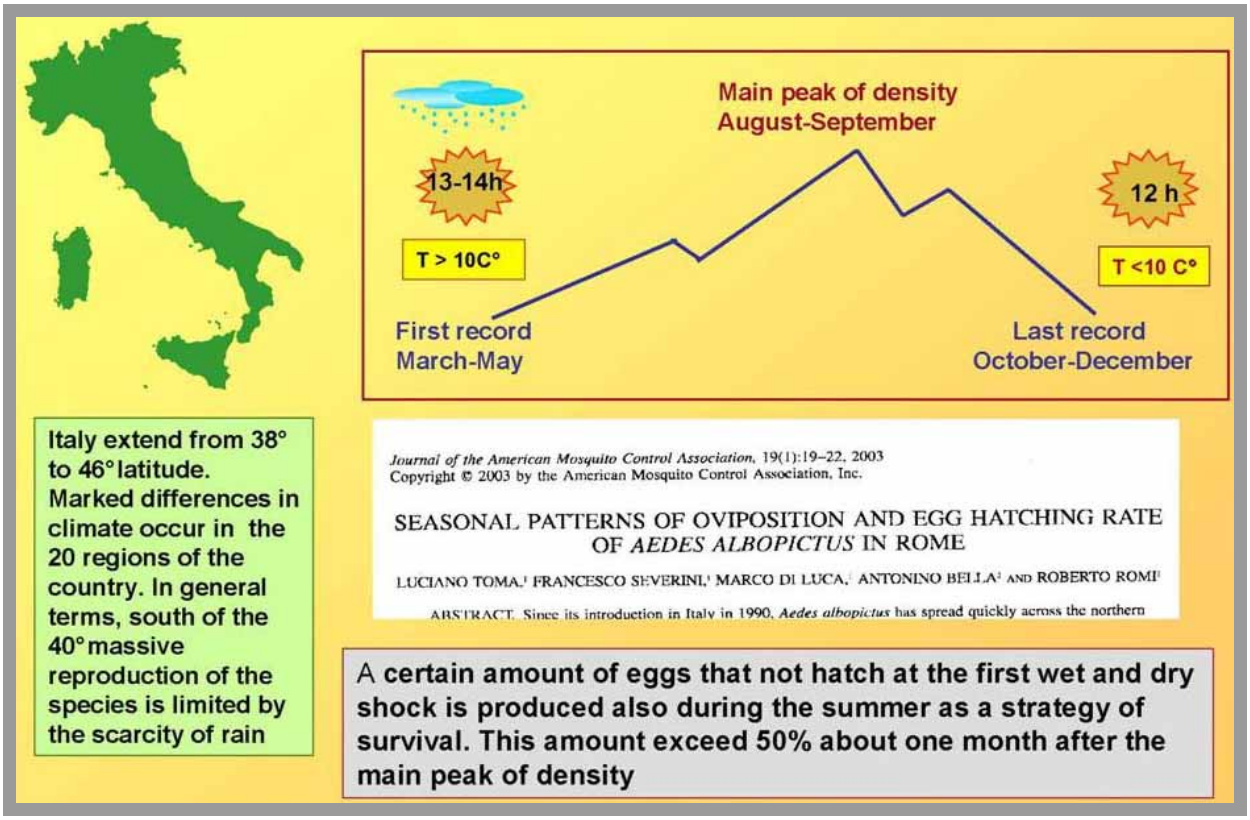


Figure 8. Seasonal dynamics of Italian populations of *Aedes albopictus*



A PowerPoint slide shown during the expert meeting listed *Aedes albopictus* breeding sites in rural and anthropic environments in Réunion, where *Aedes albopictus* colonises almost every type of small standing water. Preferred breeding sites are moderately shaded and contain clear water with organic content.

There is some variability in vector competence between populations: strains from Réunion and Madagascar are more susceptible to dengue infections than strains from southeast Asia.

They are other possible vectors of chikungunya in Europe, but no evidence to date.

The incubation and viraemia periods for chikungunya were verified after the meeting:

- The incubation period is estimated at 4–7 days; minimum is 1 day; a maximum of 12 days has been observed.
- The viraemia period is estimated at 5–7 days; a maximum of 12 days has been observed.

In conclusion, it is now recognised that *Aedes albopictus* is an important vector. The quality of information on its presence is varied, depending on the country. Several countries that are at risk have very scarce information. In order to evaluate the transmission risk, permanent surveillance of the mosquito's distribution and its populations is needed. Further research on vector competence and capacity evaluation is needed to facilitate risk modelling.

Several other autochtonous mosquitoes are suspected to act as vectors, and they should not be ignored when assessing risks and modelling disease outbreaks.

Asghar Talbalaghi: Intervention and vector control

The European Mosquito Control Association (EMCA) works towards an improvement of the quality of life by reducing mosquito numbers.

EMCA depends on international cooperation (particularly in respect to practical and scientific aspects) and skilled laboratories and entomologists.

Today's knowledge of the vector is still insufficient; appropriate and effective control strategies are needed.

There are more than 3 000 mosquito species worldwide, and over 75 in Italy. Piedmont alone has over 25 species.

There is a need to increase the knowledge of intervention strategies and evaluation methods for these strategies.

The main principle of mosquito research can be summarised in one question: 'Where are the mosquitoes coming *from?'* — and not: 'Where are they are migrating *to*?'.

Pierre-Yves Boelle: Investigating a two-wave chikungunya fever epidemic in Réunion Island, 2005–06

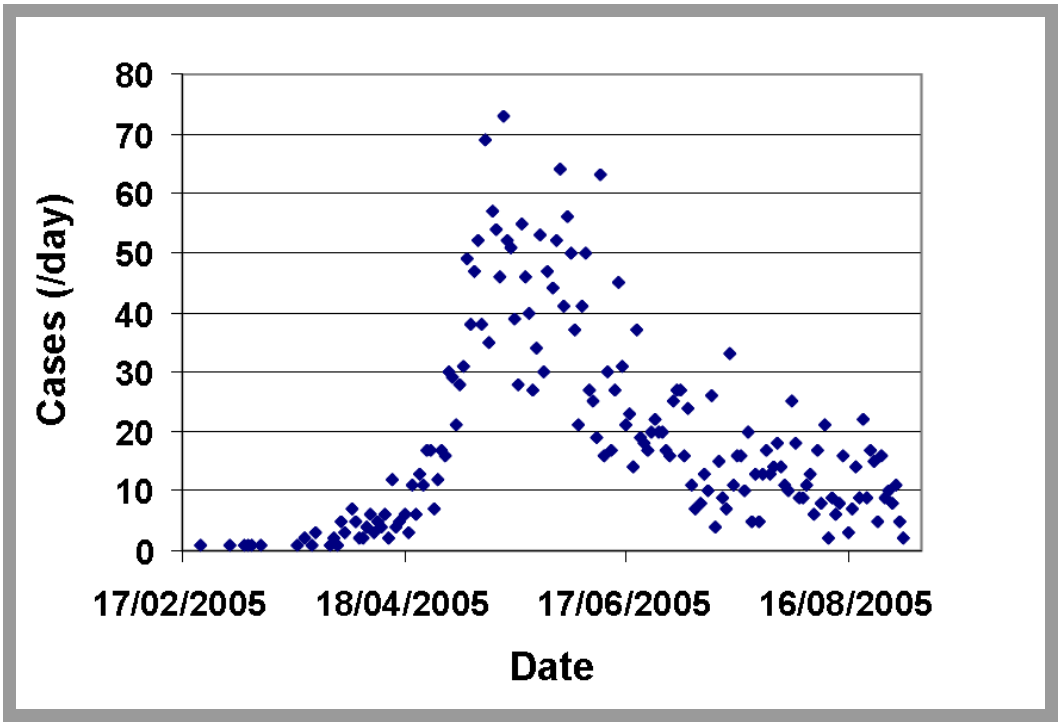
Chikungunya fever is an arthropod-borne viral disease transmitted by mosquitoes, primarily of the genus *Aedes* (as vector), namely *Aedes albopictus* and *Aedes aegypti.* It is an RNA virus belonging to the same family as Ross River fever.

Chikungunya fever was first described in Tanzania in 1953. Since then it has caused sporadic outbreaks in southeast Asia and Africa, with no obvious mosquito–human infection cycle. Typically, chikungunya is a mild disease, with acute symptoms of fever and arthralgia. The virus was first isolated in Réunion in February 2005.

Réunion is an island with a population of 780 000. The island is 63 kilometres long, 45 kilometres wide and covers 2 512 square kilometres.

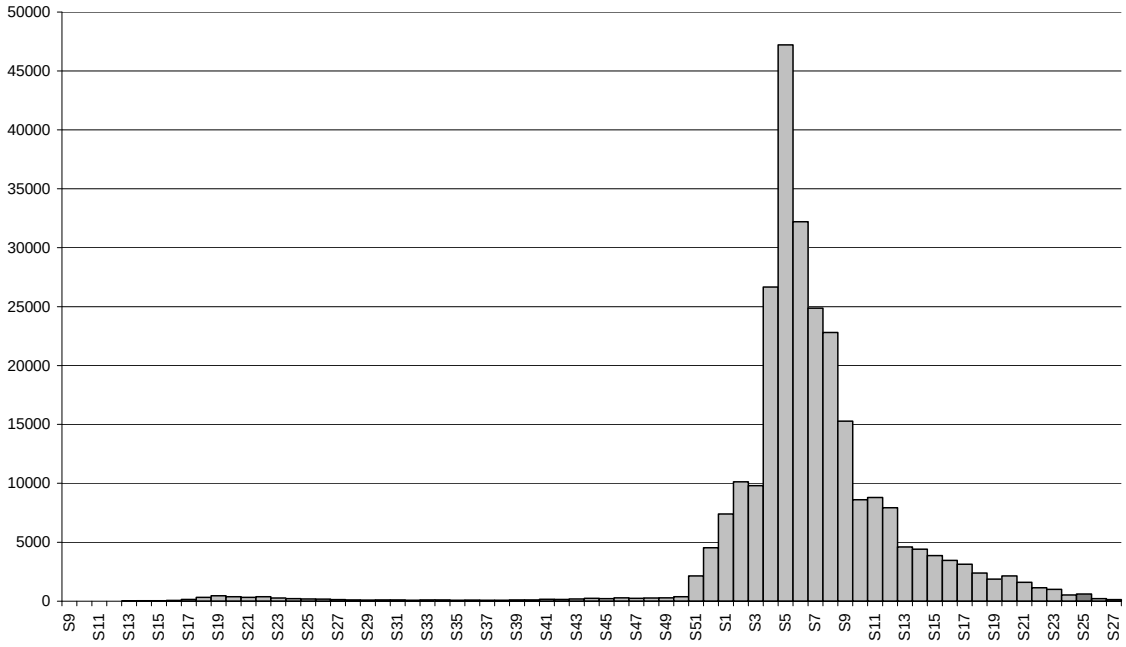
An epidemic took place in 2005 (see Figure 9 for epidemic curve).

Figure 9. Epidemic curve, chikungunya fever in Réunion Island, 2005



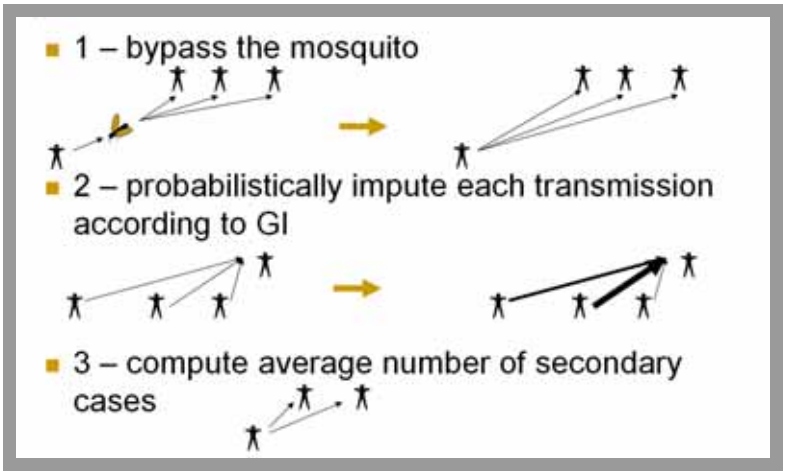
A second outbreak occurred in 2006 (see Figure 10 for epidemic curve). Figure 10 also contains the 2005 outbreak, which was very limited compared to the 2006 outbreak.

Figure 10. Epidemic curve, chikungunya fever in Réunion Island, 2005–06



As a first step, the basic reproduction number R_0 was estimated. This study used methods developed in [10], when R_0 was measured during the SARS outbreak. R_0, the basic reproduction number of an infection, is the mean number of secondary cases a single infectious person will cause in a totally susceptible population. Figure 11 shows how R_0 can describe transmission from person to person, without the need to calculate a mosquito-specific R_0 value.

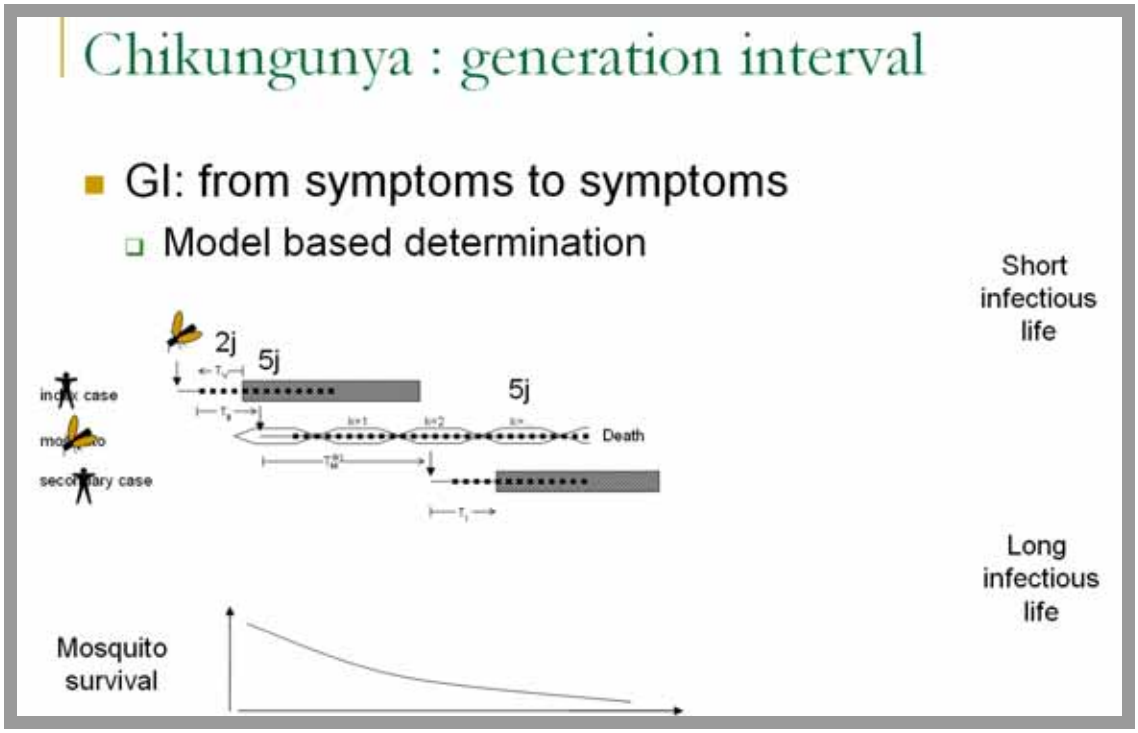
Figure 11. Calculating the basic reproduction number R_0 without a mosquito-specific R_0 value



The method for calculating R_0 relies on a concept called 'generation interval' (also sometimes called 'generation time' or 'serial time') which has many different definitions. It is defined here as the time interval between the first symptoms in the infector and the first symptoms in the infectee.

It is assumed that a person is viraemic two days after the infection occurred, and remains viraemic until five days after being infectious. See Figure 12 and 13 for the estimation procedure.

Figure 12. Estimating the generation interval



The results for the 2005 and 2006 analyses show that the value of R_0 during the initial and peak stages was between 3–4. In the time between both outbreaks, R_0 was near 1, indicating an endemic state (see Figure 14 for the estimations). Please note that the incidence curve is on a logarithmic scale. The R_0 value seems to have the same value in both outbreaks, which suggests that there is no epidemiological evidence of a change of virulence.

When analysing the epidemic, accessing the data proved to be a problem. National authorities had instant access to the data, but it took researchers approximately six months to obtain access. The 2006 data given here do not reflect the official number of cases but are numbers extrapolated from data reported by general practitioners.

Questions and comments

The calculation of R_0 is based on the epidemic curve and estimations of the generation time. Since there are only data for humans, other interesting questions, such as the consequences of the man-biting rate of the mosquitoes (the average number of bites given to humans by each mosquito per unit time) or differences in incubation time, cannot be assessed. It helps to keep in mind that this approach is not based on an epidemic model, but merely a method to estimate the generation interval.

Usually, intervention effects are measured by looking only at the number of human cases. In order to observe the effects of interventions on mosquito populations, the mosquito's egg production and its effectiveness as a vector, a mosquito-specific R_0 estimation is needed.

Figure 13. **Estimating R_0**

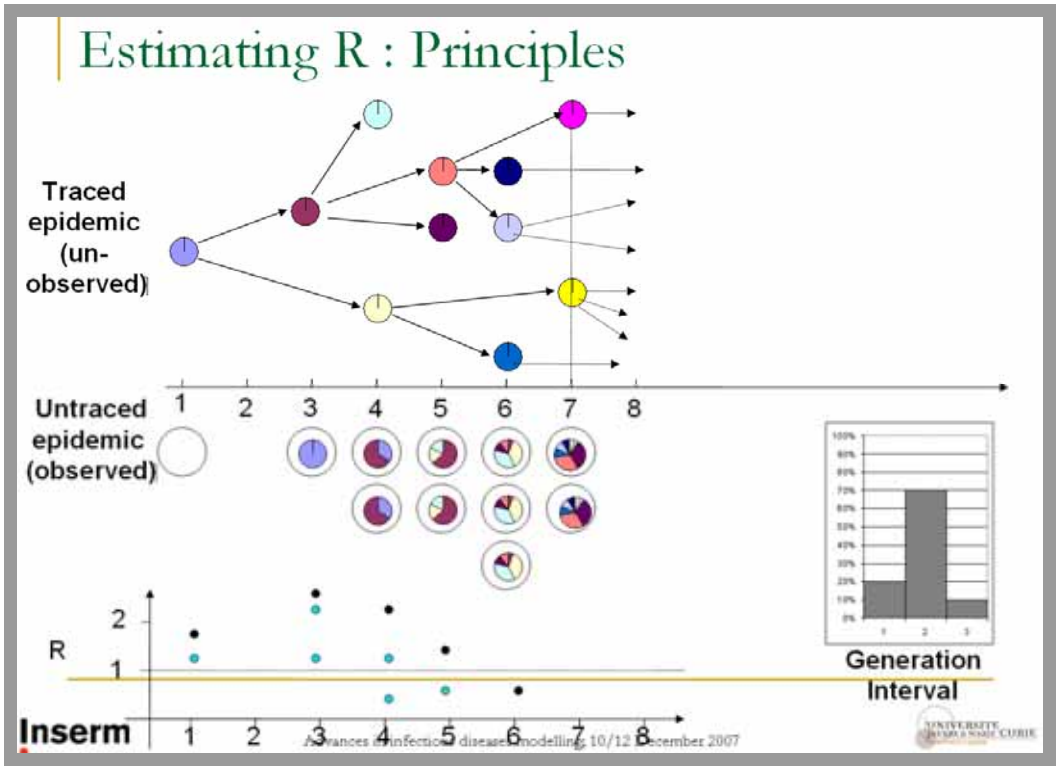
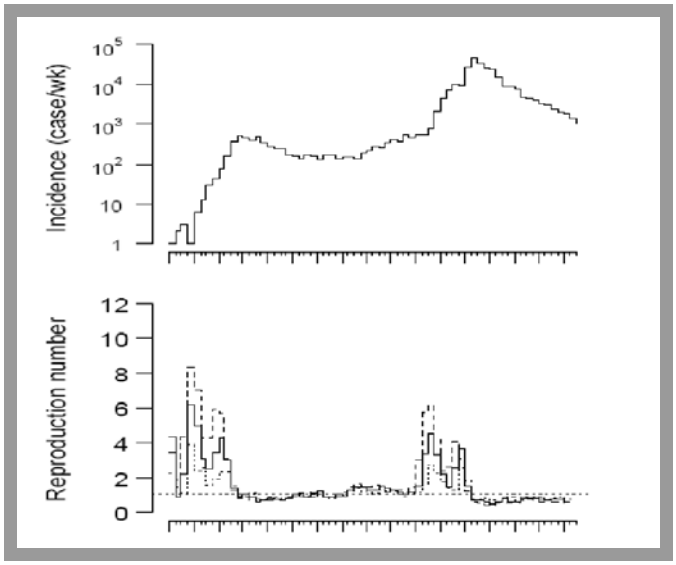


Figure 14. **Estimations of R_0 between outbreaks**



Andrea Pugliese: Modelling approaches in Italy

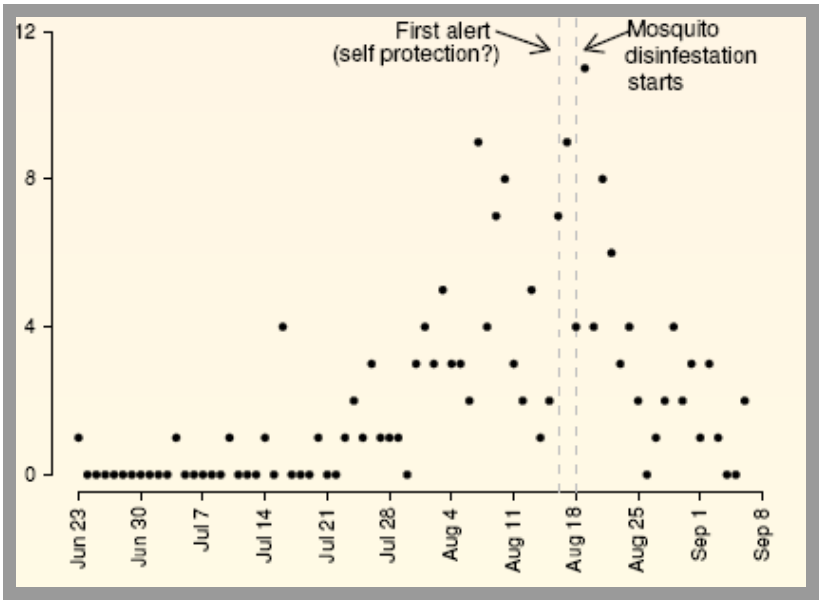
During the 2007 outbreak in Italy, a total of 214 cases was reported. A graph presented to the expert meeting showed the epidemic curve of the 2007 outbreak in the Emilia Romagna region in Italy.

The cases were concentrated in Italy's Emilia Romagna region. A total of 214 cases were laboratory-confirmed, and 161 cases occurred in the two neighbouring villages of Castiglione di Cervia and Castiglione di Ravenna. Limited local transmission also took place in the cities of Ravenna, Cesena, Cervia, Rimini, and Bologna.

The outbreaks in Castiglione di Cervia and Castiglione di Ravenna were in small villages. The epidemic began on 23 June 2007 and ended on 9 September 2007. Confirmed cases totalled 160 (161 when including the index case), and a further 31 cases were suspected. Preliminary results on seroprevalence suggest the presence of asymptomatic individuals.

Vertical transmission was suspected, yet remains unproven. The epidemic curve is shown in Figure 15.

Figure 15. Epidemic curve, chikungunya outbreak in Italy (2007)



A deterministic compartmental SEIR model (Susceptible, Exposed, Infectious and Removed) was developed to describe the epidemic and to calculate R_0. The structure is as follows: S denotes the derivative, the instant decrease or increase at time *t*.

Individuals are divided into humans (hosts, h), adult females of Aedes albopictus (vectors, v^a) and grubs (v^g).

Epidemiological states:

- S_h, susceptible host;
- E_h, exposed host;
- I_h, infectious host;
- R_h, recovered host;
- S_v^g, susceptible grub vector;
- E_v^g, exposed grub vector;
- S_v^a, susceptible adult vector;
- E_v^a, exposed adult vector;
- I_v^a, infectious adult vector;

$$
\begin{cases}
\dot{S}_h(t) &= -k\frac{\chi_h}{N_h} I_v^a S_h \\
\dot{E}_h(t) &= k\frac{\chi_h}{N_h} I_v^a S_h - \omega_h E_h \\
\dot{I}_h(t) &= \omega_h E_h - \gamma I_h \\
\dot{R}_h(t) &= \gamma I_h \\
\dot{S}_v^g(t) &= \mu\left[S_v^a + (1-q)(E_v^a + I_v^a)\right] - \delta S_v^g \\
\dot{E}_v^g(t) &= \mu q(E_v^a + I_v^a) - \delta E_v^g \\
\dot{S}_v^a(t) &= \delta S_v^g - k\frac{\chi_v}{N_h} I_h S_v^a - \mu S_v^a \\
\dot{E}_v^a(t) &= k\frac{\chi_v}{N_h} I_h S_v^a - \omega_v E_v^a - \mu E_v^a \\
\dot{I}_v^a(t) &= \delta E_v^g + \omega_v E_v^a - \mu I_v^a
\end{cases}
$$

The following parameter values are used:

parameter	description	mean (SD)	measure unit
N_h	total number of individuals	3968[1]	–
$1/\omega_h$	incubation period in humans	5 (1.32)[2]	days
$1/\gamma$	infectivity period in humans	6.5 (0.35)[3]	days
χ_h	probability of infection in humans	0.75[4]	–
$1/\omega_v$	incubation period in vectors	4.5 (1.66)[5],[6]	days
$1/\delta$	grub period	9.5 (1.6)[7]	days
$1/\mu$	lifespan of vectors	35.9 (9.96)[8]	days
q	probability of vertical transmission	0.03[9]	–
χ_v	probability of infection in vectors	0.77[5]	–
k	biting rate	–	$days^{-1}$

[1] Rezza et al., Lancet (2007)
[2] CDC, www.cdc.gov/ncidod/dvbid/chikungunya/chikvfact.htm
[3] Parola, Emerging Infectious Diseases (2006)
[4] DeFoliart, Annual Review of Entomology (1987)
[5] Vazeille et al., PLoS ONE (2006)
[6] Newton et al., The American Journal of Tropical Medicine and Hygiene (1992)
[7] Hawley et al., for Institute Pasteur (1988)
[8] Neto et al., Neotropical Entomology (2004)
[9] Fouque et al., for Institute Pasteur (1994)

Two methods are applied to calculate the value of R_0. R_0 is calculated:

- from the intrinsic growth rate;
- from the model, by fitting the epidemic curve.

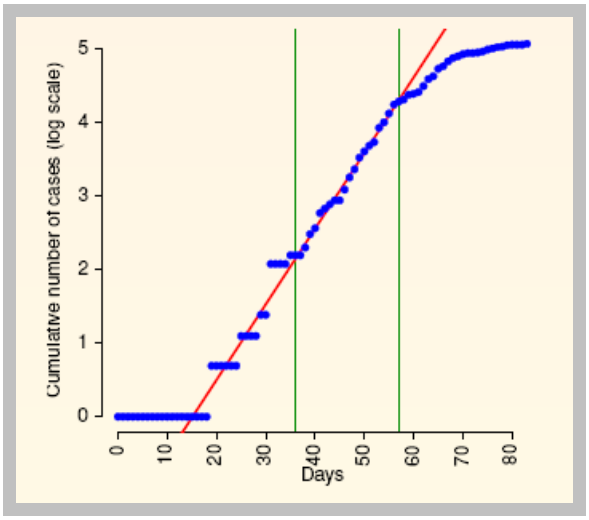
The intrinsic growth rate is based on data collected during the early epidemic phase when the effects of susceptible depletion are negligible and no intervention strategies are in place. In order to estimate the intrinsic growth rate r we need to identify the doubling time of the number of infected persons, assuming that the number of cases grows exponentially. We consider all the sets of points lasting at least seven days and having a coefficient of determination (R^2) greater than 0.98.

In this case, the R_0 of the model can be written in terms of intrinsic growth rate r, with parameters defined as before:

$$R_0 = \sqrt{\frac{(\omega_v + \mu q)(\omega_h + r)(\gamma + r)(\omega_v + \mu + r)\left[r^2 + r(\mu + \delta) + \delta\mu(1 - q)\right]}{\gamma\omega_h(\omega_v + \mu)\mu(1 - q)\left[\delta\mu q + (\delta + r)\omega_v\right]}}$$

Figure 16 shows the cumulative number of cases at the beginning of the outbreak. The cumulative numbers are on a logarithmic scale.

Figure 16. Cumulative number of cases at the beginning of the outbreak

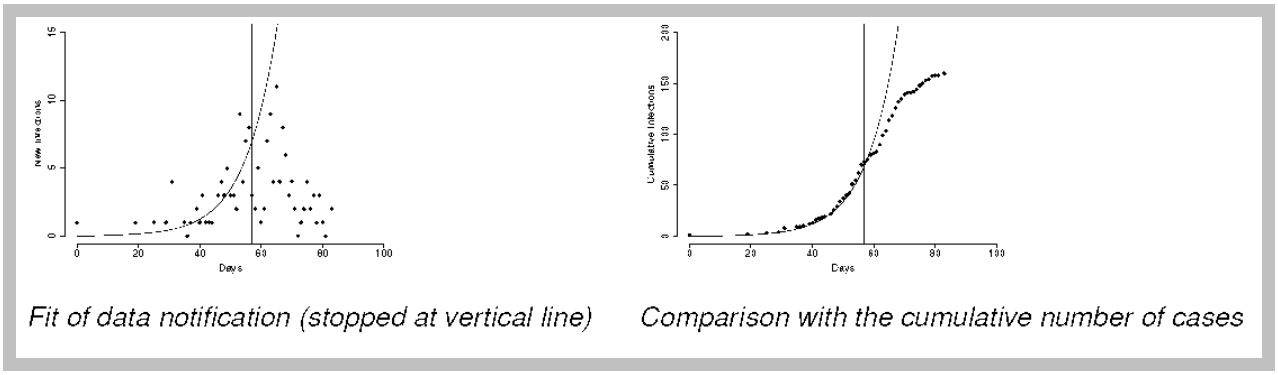


Using the second approach, which is based on fitting the model to the epidemic curve, R_0 can be estimated by the following formula:

$$R_0 = k\sqrt{N_v}\sqrt{\frac{\chi_h \chi_v}{\gamma\mu(1-q)N_h}\frac{\omega_v + \mu q}{\omega_v + \mu}}$$

For any fixed value of N_v (number of adult vectors), we search for the optimal value of parameters k and $I_{h(0)}$. Figure 17 shows the fit of the data.

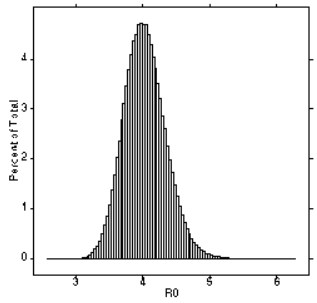
Figure 17. Fit of data notification; comparison with cumulative number of cases



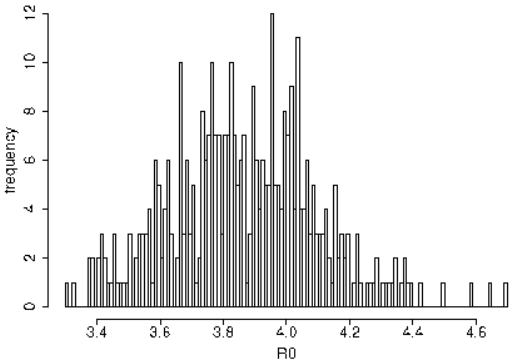
Fit of data notification (stopped at vertical line) *Comparison with the cumulative number of cases*

Both methods show similar values of the R_0 values (around 4) for the Réunion outbreak.

method	mean	R_0 CI (95%)
intrinsic growth rate	4.03	(3.42, 4.64)
epidemic curve fitting	3.87	(3.40, 4.34)



intrinsic growth rate



data fitting

In order to measure the effects of interventions, the changes of R_0 during an outbreak can be estimated. Similar calculations were performed during the SARS outbreak in 2002.

R_e at any time t has been computed, using a Bayesian method [10,11,12] as

$$\begin{aligned} R_e(t) &= X_t/n_t \\ &= n_t \sum_k (n_k - 1\{k=t\})\, p_{tk}/n_t \\ &= \sum_k (n_k - 1\{k=t\}) \frac{w(k-t)}{\sum_i (n_i - 1\{i=k\})\, w(k-i)} \end{aligned}$$

where

- n_t is the number of cases with onset in week t
- X_t is the total number of cases generated from cases with onset in week t
- p_{tk} is the probability that a case with onset in week k was generated by a case with onset in week t
- w is the probability density function of the generation interval GI, roughly the time for the cycle human–vector–human transmission
- $1\{i=k\} = 1$ if $i=k$, 0 otherwise

[10] Wallinga et al., American Journal of Epidemiology (2004)
[11] Cauchemez et al., Emerging Infectious Diseases (2006)
[12] Boelle et al., Vector–Borne and Zoonotic Diseases (2008)

The following parameters are used:

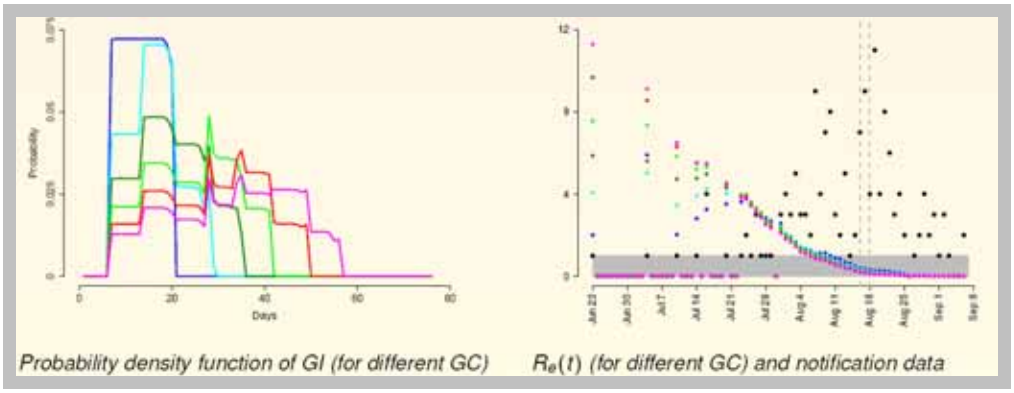
- Gonotrophic Cycle (GC): 7 days[13].
- We consider $1, 2, 3, 4, 5, 6$ as possible numbers of GC, according to the lifespan of the mosquitoes[13]
- $GI = -T_V + T_B + T_I + T_M$, where

parameter	interpretation	value (in days)
T_V	Viremia before symptom onset	1 with probability $2/3$ 2 with probability $1/3$[14]
T_B	Time at which a bite occurs, during human infectiousness	Discrete uniform distributed in $(1,7)$[14,15]
T_I	Mean duration of the incubation period for humans	Gamma distributed with mean 3 and SD 1.3[14,16]
T_M	Time from initial contaminating bite to a transmission bite in a mosquito	$7, 14, \ldots, 42$ (depending on the number of GC)

[13] Neto et al., Neotropical Entomology (2004)
[14] Boelle et al., Vector–Borne and Zoonotic Diseases (2008)
[15] Parola, Emerging Infectious Diseases (2006)
[16] CDC, www.cdc.gov/ncidod/dvbid/chikungunya/chikvfact.htm

The fluctuation of R_0 is shown in Figure 18.

Figure 18. Fluctuation of R_0



The values for R_0 show that the peak occurred when interventions were used. There is a need to study what R_0 would have looked like if no interventions had been implemented.

The decrease of R_0 can be due to a spontaneous decline in the contact rates (e.g. due to behavioural changes in human population, self protection) or the number of mosquito populations. The advanced decay of R_0 in regard to the time of intervention is in line with the culling of mosquitoes before they have a chance to infect humans.

Questions and comments

During the outbreak, 5 % of the population were infected. There is a need to consider the effects of interventions. Available data only cover the human population. Looking at changes in the mosquito populations might also explain the decrease of R_0.

Further research is needed on the effects of report delays and possible changes of generation intervals that were imposed by interventions. A better understanding is needed of how changes of the population size affect the calculations. The Réunion outbreak occurred during a holiday period when it is more difficult to estimate the size and movement of a population.

Nicolas Bacaer: The basic reproduction number for vector-borne diseases with a periodic vector population

This study aims to estimate R_0 with different methods and assumptions that also include factors such as rainfall, temperature and mosquito density.

There are obvious similarities to the analysis of other diseases. The outbreak of leishmaniasis in Morocco in 2005 called for the application of methods originally developed to assess the influence of seasonality on epidemics. The analysis of outbreak data should also include the interpretation of numerical values of R_0.

The basic approach in modelling is to split the human and mosquito population into different SEIR stages. One possibility is as follows:

$$S(t),\ E(t),\ I(t),\ R(t)\text{: humans}$$
$$S'(t),\ E'(t),\ I'(t)\text{: mosquitoes}$$

$$P = S(t) + E(t) + I(t) + R(t)$$
$$P'(t) = S'(t) + E'(t) + I'(t)$$

$$\frac{dS'}{dt} = \lambda(t) - \beta\, S'(t)\,\frac{I(t)}{P} - \mu\, S'(t)$$
$$\frac{dE'}{dt} = \beta\, S'(t)\,\frac{I(t)}{P} - (\gamma + \mu)\, E'(t)$$
$$\frac{dI'}{dt} = \gamma\, E'(t) - \mu\, I'(t)$$
$$\frac{dS}{dt} = -\beta\, I'(t)\,\frac{S(t)}{P}$$
$$\frac{dE}{dt} = \beta\, I'(t)\,\frac{S(t)}{P} - \delta\, E(t)$$
$$\frac{dI}{dt} = \delta\, E(t) - \alpha\, I(t)$$
$$\frac{dR}{dt} = \alpha\, I(t)$$

The following parameter values were used:

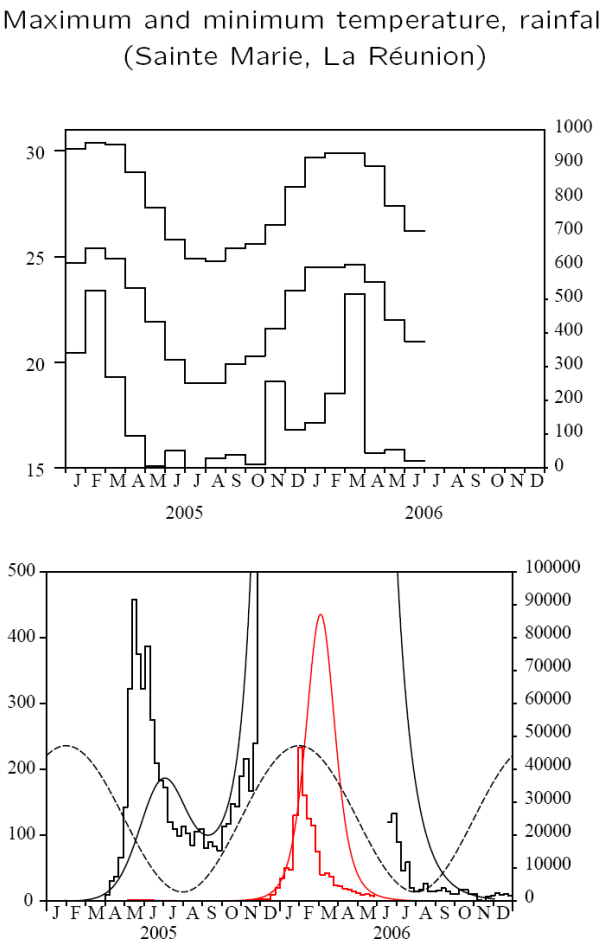
fixed parameters		
latent period in vectors	$1/\gamma$	7 days
life expectancy of vectors	$1/\mu$	1 month
latent period in humans	$1/\delta$	4 days
infectious period in humans	$1/\alpha$	7 days
time between two bites	$1/\beta$	4 days
population of La Réunion	P	785,000
peak of vector population	ϕ	$\frac{2\pi}{12}$ (beginning of February)

Adjusting for a periodic vector population, the population of the mosquitoes P´ is assumed to be following a cosine curve, with the periodicity of one year.

$$P'(t) = P'_0(1 + \varepsilon\cos(\omega t - \phi))$$
$$P'_{\max} = P'_0(1 + \varepsilon)$$
$$P'_{\min} = P'_0(1 - \varepsilon)$$

Optimal values are gained by varying t_0, p_{min} and p_{max} in order to fit the incidence.

Figure 19. 2005 and 2006 (red) outbreaks



In Figure 19, the solid line represents the fit to data for the 2005 outbreak; the scale is shown on the right. The red solid line represents the 2006 outbreak (left scale). The dashed line shows the periodicity of the mosquito population.

Different ways of receiving an R_0 estimate around 3.4

Do a linearisation of the following system of differential equations near the disease-free situation where S(t)=P and S´(t)=P´(t):

$$\frac{de'}{dt} = \beta\, P'(t)\,\frac{i(t)}{P} - (\gamma + \mu)\, e'(t)$$
$$\frac{di'}{dt} = \gamma\, e'(t) - \mu\, i'(t)$$
$$\frac{de}{dt} = \beta\, i'(t) - \delta\, e(t)$$
$$\frac{di}{dt} = \delta\, e(t) - \alpha\, i(t)$$

There are several methods to solve this system of equations; one method was developed by Floquet and uses a next-generation matrix.

$$\frac{dX}{dt} = \begin{pmatrix} -(\gamma+\mu) & 0 & 0 & \frac{\beta}{P}\frac{P'(t)}{R_0} \\ \gamma & -\mu & 0 & 0 \\ 0 & \beta & -\delta & 0 \\ 0 & 0 & \delta & -\alpha \end{pmatrix} X(t)$$

$$X(0) = 1_{4,4}$$

$$\text{spectral radius of} X(T) = 1\ , \quad T = 2\pi/\omega$$

The second approach was developed by McKendrick.

$$\begin{pmatrix} e'(t,0) \\ i'(t,0) \\ e(t,0) \\ i(t,0) \end{pmatrix} = \int_0^\infty \begin{pmatrix} 0 & 0 & 0 & \frac{\beta\, P'(t)}{P}\, e^{-\alpha x} \\ \gamma e^{-(\gamma+\mu)x} & 0 & 0 & 0 \\ 0 & \beta e^{-\mu x} & 0 & 0 \\ 0 & 0 & \delta e^{-\delta x} & 0 \end{pmatrix} \begin{pmatrix} e'(t-x,0) \\ i'(t-x,0) \\ e(t-x,0) \\ i(t-x,0) \end{pmatrix} dx$$

$$R_0\, \psi(t) = \int_0^\infty K(t,x)\, \psi(t-x)\, dx$$

$$\psi(t+T) = \psi(t)$$

The third approach uses cyclicity and includes Fourier transforms and properties of sinusoidal curves.

$$\frac{R_0}{z_0} - 1 = 2\,\Re\, \cfrac{\varepsilon^2/4}{\cfrac{R_0}{z_1} - 1 - \cfrac{\varepsilon^2/4}{\cfrac{R_0}{z_2} - 1 - \cfrac{\varepsilon^2/4}{\cdots}}}$$

$$z_k = \frac{\beta^2\, (P_0'/P)\, \gamma\, \delta}{(\alpha + k\mathrm{i}\omega)(\mu + k\mathrm{i}\omega)(\gamma + \mu + k\mathrm{i}\omega)(\delta + k\mathrm{i}\omega)}$$

$$R_0 \underset{\varepsilon \to 0}{\simeq} z_0 + \frac{\varepsilon^2}{2} \Re\left(\frac{z_0\, z_1}{z_0 - z_1}\right)$$

Remark: $R_0 \simeq 3.4$ but $z_0 \simeq 3.9$.

The last calculation shows that numerical methods give different values of R_0, in this case with deviations of as much as 0.5 in magnitude.

As expected, the three numerical methods yield the same value for R_0.

In summary, the standard references on epidemic modelling [11, 12] do not explain how R_0 can be defined and computed in epidemic models with periodic coefficients. Such periodic coefficients are necessary to take seasonality into account. Seasonality played an important role during the chikungunya epidemic in Réunion because the epidemic lasted two years and continued over the winter months. Seasonality was less important in the epidemic in Italy because the epidemic was very short and had come to an end in August. Methods to define and compute R_0 in epidemic models with periodic coefficients were introduced in the following references [2, 13-15]. (Note by ECDC: Methods with seasonal components and periodic coefficients in mathematical models have been used since 1998 and were first applied to childhood diseases, especially measles [16]).

Questions and comments

Questions were raised regarding the use of the larvae population size instead of a cosine curve which represents the seasonality of the population size. This was not possible due to insufficient data; therefore a cosine curve was fitted to match the epidemic curve.

Discussion

It is essential to combine different knowledge elements in order to create a complete picture of virus transmission. The following measures and questions are under consideration:

- Mapping: Where exactly will mosquitoes become permanent hosts, what is the habitat of the mosquito, where does it live, etc. Continuation of the mapping project at the EU level.
  - Interpolate climate/weather data and assess the impact on mosquito populations.
  - Accuracy depends on the number of parameters and their respective accuracy.
  - A minimum mosquito population size is required before mosquitoes can become effective vectors.
  - Complicated mapping process when data is layered.
  - Do variables depend on temperature?
- Production of monthly vector density maps for *Aedes albopictus* for EU Member States.
- Which questions can be addressed with models and how can modelling tools be used most efficiently?
  - The endemicity of the virus.
  - When do mosquitoes become active?
  - Application of population dynamic models.
  - Impact of interventions.
- The sampling of *Aedes albopictus* populations requires accumulated data, e.g. the number of larvae per population. Need for some sort of basic truth/fact/data.
- What parameters determine whether mosquitoes will appear in a given area or not?
- Use data with geographic projections and then determine the size of the population where outbreaks occur.
  - Can be used as an indicator.
- Traps cannot provide precise information about mosquitoes because natural habitats cannot be compared with traps.
  - Need to study the efficacy of maps and compare the results from trap studies with studies on natural habitats.
  - Assessment of the sampling bias.
- Consensus on what needs to be collected and how.
  - Make sure researchers are collecting in the field.
- Need to differentiate between the risk of importation of the vector and the risk of vector establishment.
- Data sharing:
  - During an outbreak: nationally or internationally?
  - Seasonal data.

The exchange of data during the Italian and Réunion outbreaks was rather slow. In Réunion, people were not always comfortable with sharing surveillance data.

- It is important to know what data have been reported; in Réunion, data from visits by general practitioners were extrapolated. Is there a need for more accurate data collection systems?
  - Better access to ground level data.
  - Who should collect the data?
  - Estimation of the reporting delay.
- Funding should be available to pay entomologists to enter outbreak areas and follow the vector population.
- Virus transmission, its impact and extent.
  - Identification of threshold leading to cessation/increase of cases.
  - What happens when the threshold has been reached?
- Focusing primarily on short-lived epidemics is not helpful; very useful to gain knowledge from long-term seasonal data.

- Unavailable/missing key data are on:
  - seasonal activity;
  - climate variables (what limits the spread to certain areas of Europe?);
  - biting rates and what influences them; and
  - vector distribution over time.
- Complexity of mathematical models.
  - Many parameters give a consistently good fit to data. Difficult to know the minimum set of necessary parameters.
  - Model comparison.
  - Assumptions in the random effects in models; what is the effect of changing these?
  - Accuracy of the Ross model.
- Standardised way to measure vector density in order to provide the basis for a mosquito prediction system at the European level.
- Establish a methodology for estimating mosquito biting rates.

Conclusion

This meeting brought together modellers, entomologists and public health officials from several European countries. Presentations during the meeting covered both entomology and modelling. The following conclusions were drawn.

Modelling for chikungunya outbreaks can be performed:

- by using an epidemic model integrated in the calculations, or
- by analysing only the crude data.

At the moment, the available data — often only estimations interpolated from other sources — only cover human cases. A consensus needs to be reached on how data will be shared in the future, both nationally and internationally.

Model development and model structures, including underlying assumptions for different calculation methods (e.g. models with random components, extrapolated data), need to be specified and transparent when modelling outbreaks. Additionally, reporting the basic reproduction number R_0 for chikungunya can be very misleading since its estimated value depends on both the available data *and* the underlying assumptions of the used models, and thus varies considerably. There is only one way to address this problem: modellers need access to reliable data in order to perform calculations with their preferred model. Similar problems are encountered when pandemic influenza is concerned. Simply reporting an R_0 value will be of dubious value and not helpful for countries that conduct their own modelling. This implies difficulties in assessing whether the epidemic is under control and when the infection will die out, e.g. when $R_0 < 1$.

Additional model development is needed to include the effects of imposed interventions in the models and to assess how interventions are related to the size of the mosquito population.

The largest gap in knowledge at this moment concerns data related to the vector. Some models have entirely bypassed the vector and estimated seasonality from an epidemic curve, or have included an estimated seasonal vector density in the population with some predetermined shape. In order to provide more precise calculation results, the size of the vector population needs to be determined and human cases have to be included. This would make it possible to estimate the lapse in time between the first intervention measures and a noticeable reduction of human cases.

In order to assess the vector population, several criteria have to be met, including standardised reporting, secured funding, consistent mechanisms for data input, data storage, and data distribution and access. In this context, the sampling bias caused by traps needs to be assessed. Once the size of a vector population is determined, modellers and entomologists can *jointly* develop models that will make it possible to follow an epidemic in real time.

Follow-up meetings on chikungunya or other vector-borne diseases are possible. ECDC should invite multidisciplinary participants in order to identify the gaps in knowledge in the various fields and foster multidisciplinary approaches.

Participants

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Francis Schaffner	Institute of Parasitology, University of Zurich, Switzerland
Jan Lundström	Uppsala University, Sweden
Andrea Pugliese	University of Trento, Italy
Asghar Talbalaghi	EMCA, Italy
Tommi Asikainen	Scientific Advice Unit, ECDC
Denis Coulombier	Preparedness and Response Unit, ECDC
Evelyn Depoortere	Preparedness and Response Unit, ECDC
Piotr Kramarz	Scientific Advice Unit, ECDC
Lara Payne	Preparedness and Response Unit, ECDC
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Agenda

0900 – 0910	Welcome talk. Piotr Kramarz, deputy head of unit, Scientific Advice Unit
0910 – 0915	Introduction of participants. Tommi Asikainen
0915 – 0930	Overview of available parameters and the public health need of chikungunya modelling. Tommi Asikainen
0930 – 0940	ECDC activities concerning chikungunya. Tommi Asikainen
0940 – 1010	Understanding environmental determinants for establishment and spread of *Aedes albopictus*. Jolyon Medlock
1010 – 1030	Coffee Break
1030 – 1055	Entomology. Francis Schaffner
1055 – 1140	Intervention (vector control). Asghar Talbalaghi
1140 – 1210	Modelling approaches in France. Pierre-Yves Boelle
1210 – 1320	Lunch
1320 – 1350	Modelling approaches in Italy. Andrea Pugliese
1350 – 1420	Basic reproduction number for vector-borne diseases with a periodic vector population. Nicolas Bacaer
1420 – 1450	Discussion on modelling for chikungunya
1450 – 1510	Coffee break
1510 – 1630	Closing remarks: identifying research needs, data-sharing issues. Tommi Asikainen