An interdisciplinary approach to controlling chikungunya outbreaks on french islands in the south-west indian ocean

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RÉSUMÉ • L'épidémie de chikungunya dans le sud de l'océan Indien en 2005-2006 s'est traduite par une forte morbidité et une forte mortalité. Les autorités françaises ont alors mis sur pied une cellule chargée de la coordination de la riposte à l'épidémie composée de scientifiques appartenant à divers domaines : épidémiologie, santé publique, entomologie, virologie, sociologie, santé animale, santé communautaire et médecine hospitalière. Cette cellule de coordination avait pour mission d'élaborer et de proposer aux autorités des axes de recherche afin de mieux comprendre la maladie et l'épidémie, et d'éclairer les autorités dans leur réponse à l'épidémie. Cet article rend compte de l'expérience de cette cellule pendant les deux années de son existence et des tous premiers résultats dans ses domaines de compétence. Il souligne également les zones de non-connaissance qui persistaient lors de la dissolution de celle-ci.

MOTS-CLÉS • Chikungunya. Océan indien. Cellule de coordination. Recherches. Résultats.

FRENCH RESEARCH COORDINATING TASK FORCE FOR CHIKUNGUNYA AND DENGUE

ABSTRACT • The outbreak of chikungunya that occurred on French Island territories in the southwest Indian Ocean in 2005 and 2006 caused severe morbidity and mortality. In the aftermath, French authorities set up a scientific task force including experts in epidemiology, public health, entomology, virology, immunology, sociology, animal health, community and hospital medicine. The mission of the task force was to conceive and propose research programs needed to increase understanding of the disease and epidemic and to help public health officials in improving epidemic response measures. The purpose of this article is to describe the findings of the task force at the end of its two-year existence and initial outcomes in the the areas studied. Discussion emphasizes topics requiring further study.

KEY WORDS • Chikungunya. Indian Ocean. Task force. Research. Findings.

Introduction

In an East African language, chikungunya means "that which bends up", or "to walk bent over" because joint pains are a major feature of both the acute and the chronic phases of the disease. Chikungunya (CHIK) emerged in the southern Indian Ocean islands in 2005 and 2006, affecting 30 to 75% of the naïve local populations. This epidemic that was the first that occurred in the highly developed society of Reunion (1, 2, 3), caused severe morbidity and mortality and urged the French authorities to set up a task force composed by scientists belonging to the main relevant domains involved by the phenomenon: epidemiology, public health, entomology, virology, immunology, sociology, animal health, community and hospital medicine. The task force had to conceive and propose needed researches to increase understanding of the disease and of the epidemic and to perform and/or trigger collaborative research programs to enlighten health authorities in their response. This article presents a two year process and first results in all area it covered. It also points out topics where knowledge is still lacking.

Spread of chikungunya

Molecular epidemiological studies of this epidemic (4, 5) confirmed that the same strain had circulated throughout the Indian Ocean region from early 2005, before being detected in October 2005 in continental India, where the disease had been absent for 32 years then in late 2006 and 2007 in Malaysia, Indonesia, Sri Lanka, Maldives islands. An Italian outbreak originated from a traveler coming back from India occurred in summer 2007 involving about two hundreds persons.

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Clinical features of the disease

Clinical Manifestations

Peripheral joints manifestations often relapsing, although rarely affecting children (6), were reported in two third of a series of 158 cases out of 662 military troops in Reunion Island between January 2005 and June 2006 (7). Ankles, wrists, fingers were the joints most commonly affected. In Reunion, arthralgias persist in 57% of patients, 12 to 18 months after the onset (8).

Rash affected about 40-50% of cases and usually lasted 5 to 10 days (9, 10). It appeared mainly on the trunk and limbs, but also occurred as an oedema on the face, or in children as a bullous eruption with isolation of CHIK virus in blister fluid. Most commonly the skin eruption was a pruriginous maculopapular rash, an exanthema with patches of healthy skin, but localised petechiae and gingivorrhagia was seen particularly in children. Peeling remained rare in adults as itching was reported in 20 % of cases and could be isolated. In most cases, the outcome was rapidly favourable, sometimes with remaining dyschromic patches or scaling (11).

Emerging and severe presentations

Previously undescribed severe clinical forms were reported in Reunion, including peripartum mother-to-infant transmission and meningoencephalitis (sometimes in newborns), hepatic failures and deaths (12). Common hematologic abnormalities in the acute phase included deep lymphopenia and thrombocytopenia that may be associated with bleeding. Levels of hepatic enzymes were commonly increased and viral loads were remarkably high – frequently above 10^9 virus particles per millilitre of serum.

Among patients over 10 years of age there were 273 life-threatening cases, 59% of which affected elderly people (>65 years). CHIK virus infection was confirmed in 246 of these cases. One hundred of these patients had co-morbidities and 27% of the patients with documented severe infection died. Among severe manifestations reported in adults, were 5 meningoencephalitis, Guillain-Barré syndromes, (13), serious liver damage, heart failure and 12 cases of other organ failures (cerebral, renal, multiorgan, respiratory, acute myocardial infarction). The median age at the time of death was 79 years (range 0 to 102 years), and the male-female sex ratio was 0.95. In Reunion, it is estimated that 252 deaths were related to the epidemic (14). In Mauritius, the number of deaths from January through June 2006 increased by 16.7% over the number of deaths in 2005, and 19.8% more deaths occurred among persons over 60 years), corresponding to 743 excess deaths during the epidemic (15).

Chikungunya in pregnancy and infants

The epidemic revealed for the first time 43 confirmed materno-neonatal transmission in the perinatal period. In a retrospective descriptive study conducted in five neonatal units between March 2005 and April 2006, CHIK infection was confirmed by RT-PCR or specific serology in mothers and thirty-eight neonates newborns (16). All mothers but two presented signs of CHIK during perinatal period. All neonates experienced symptoms from D3 to D7. The mean interval between onset of maternal illness and onset of neonatal illness was 5 days (range, 3–9). The most frequent clinical signs in neonates were prostration, fever (79%), pain (100%), rash (82%), peripheral oedema (58%). Thrombocytopenia (76%), lymphopenia (47%), decreased prothrombin value (65%) and elevation of aspartate aminotransferase (77%) were also noticed. In 61 % neonates, the full recovery occurred within 2 weeks. Among the others, complications included seizures (6), hemorrhagic syndrome (6) and hemodynamic disorders (10). One infant eventually died at day 6 (necrotizing enterocolitis and *Klebsiella pneumoniae* septicaemia). Half of the infected children required mechanical ventilation, half had signs of cerebral oedema, and a quarter of infected children had abnormal development. RT-PCR in cerebrospinal fluid was positive in 22 of 24 cases with abnormal findings on brain magnetic resonance imaging (14 of 25) with white matter lesions or intraparenchymal haemorrhages or both.

From molecular biology to clinical trials

Cloning the chikungunya ORFeome – All the virus protein-coding sequences were cloned and introduced into expression vectors, with fusion in order to add a short amino acid tag recognized by monoclonal antibodies and were expressed in mammalian cells been followed via their molecular tag. Thirty-three interactants were identified. Protein interaction map are also generated for CHIK-related viruses in an attempt to provide a comprehensive molecular support to viral replication and associated syndromes.

Production of chikungunya virus infectious clones - Infectious cDNA clones of virus have been constructed and characterized using a recent isolate from Reunion (17). Comparison of the growth kinetics and infection rates, indicates that the infectious clone has retained the viral phenotypes of the original isolate. Several infectious clones expressing green fluorescent protein were also characterized in cell culture and in *Aedes* mosquitoes. The development of these authentic infectious clones will enable targeted studies of the molecular determinants of infection, pathogenesis and transmission competence by *Ae. aegypti* and *Ae. albopictus* mosquitoes. Cloning of human monoclonal antibodies to CHIK virus is currently performed. Neutralizing antibodies will have to be tested against several viral strains in vitro and in vivo.

Human immune immunoglobulin production for therapeutic purposes is very promising but their availability is uncertain partly due to regulatory requirements, which include complete recloning of the antibodies in particular lineages. Several hundred liters of blood from selected donors who recovered from CHIK were collected and batches of immune immunoglobulines were prepared that will soon be tested in animals.

Macaca fascicularis is a promising animal model (18) used to characterize the biological and clinical outcomes of the infection in terms of early and late immunopathologic events, to explore anatomical and tissular sites of early and possible late viral replication, and to identify the origin of the persistent arthralgias associated with this disease. Experimental virus infection of long-tailed macaques is followed by clinical signs and viral and immunological features similar to those seen in humans.

Research on drugs with antiviral properties –The task force adopted a strategy aimed at identifying new therapeutic tools and screened drugs already marketed in other indications, in the portfolios of antibiotics, antimalarial and antiviral drugs, for their antiviral properties for *ex vivo* screening. The discovery of the *ex vivo* antiviral properties of chloroquine prompted a randomized double-blind placebo-controlled human clinical trial in Reunion, with the aim of evaluating it in the prevention and treatment of CHIK. As the epidemic was declining, it was not possible to enroll the initially planned number of patients. An interim analysis on 75 patients in the curative protocol showed good tolerability and no serious adverse effects, but failed to demonstrate the superiority of chloroquine over the placebo. In late 2006, efficacy of preventive treatment with chloroquine was assessed in *Macaca fascicularis* and showed no benefit in terms of antiviral activity (19).

Towards a vaccine? A vaccine for CHIK was developed in the 1980s by the United States Army Medical Research Institute for Infectious Diseases from a live attenuated strain of Asian origin. Preclinical studies and phase II trials had been initiated among 200 healthy American army volunteers (20) with satisfactory seroconversion rates and neutralizing antibody titers, but development was stopped. When we obtained batches of this vaccine in 2007, it no longer met the demands of the European Medicines Evaluation Agency. Requalification of the candidate vaccine was planned to be achieved in 2009. In the macaque model, it confers protection against recent Reunion strains and antibodies produced will be tested *in vitro* for their capacity to neutralize infection by Reunion strains. The trials will first involve human safety tests, with no exposure to the risk of infection.

Ecology of chikungunya

Mosquito Vectors: An entomological situation compatible with future re-emergence in urban and peri-urban areas

CHIK and dengue viruses (21) are transmitted by mosquitoes *Ae. aegypti* and *Ae. albopictus* that are adapted to urban and peri-urban environments (22). Larvae are ubiquitous in domestic, peri-domestic and natural niches, rendering vector control difficult. The Reunion CHIK crisis revealed a severe paucity of data on the culicidian fauna of the island and, more largely, of the southwest Indian Ocean region. Entomological data are even more fragmentary in Mayotte Island, where 36 species of mosquitoes have been reported.

Viral isolation and RT-PCR-based studies done on adults mosquitoes collected in Reunion, confirmed the role of *Ae. albopictus* as the primary vector since the virus was found in 24 pools among about 600 tested yet. Moreover, the virus was detected from two pools of larvae among 700 tested, confirming that vertical transmission occurs in epidemic conditions. In order to estimate vector competence, mosquito populations from Reunion and Mayotte were orally infected with CHIK virus strains isolated in Reunion and compared to Asian and African populations. In each case, infection rates observed in laboratory exceeded 80%, demonstrating that *Ae. albopictus* strains from Indian Ocean are highly receptive to CHIK virus (23).

Aedes mosquitoes are present in all inhabited areas and "ravines", until an altitude of 1200 meters in summer and 800 meters in winter (24). Surveys showed that one-third of water samples contained *Ae. albopictus* larvae, two mains peaks of agressivity : from 8 to 10 *a.m.* and from 4.30 to 7.30 *p.m.* and demonstrated that the species are mainly exophagic with 86% of bites outdoors. Laboratory studies on larval development show that development time and survival are highly dependent upon the temperature, ranging from 8 to 35 days and that more than half of females live for more than 4 weeks at usual temperatures that also influences the number of eggs, which ranges from 50 to 100 per batch.

Entomological impact of the larval habitat destruction campaign by citizens

Mobilization of citizens were key intervention measures, with a high media coverage (October 28-29, 2006; February 17-18, 2007; October 2007). The main objectives were to alert, inform and educate population on the role of mosquitoes and on the need for mechanical destruction of domestic and peri-domestic larval niches. That program was based on 10 key-points and entomological indices were measured in 7 locations of Reunion before, then 2, 15 and 30 days after the operation held on October 28-29, 2006. Analyses showed a marked reduction in the risk index (number of recipients containing *Ae. albopictus* larvae per 100 households) immediately after the campaign, but it rose again one month later following a rainy period.

Vectors in Mayotte - It is assumed that both *Ae. albopictus* and *Ae. aegypti*, played a role in transmission, with a secondary role attributed to *Ae. simpsoni*. Virus was not detected in mosquitoes during the 2006 epidemic. A distribution map and a study of the larval niches of these species are ongoing.

Role of animals

Primates act as reservoir in Africa. Reunion is free of monkeys, Mayotte is hosting lemurs, Mauritius has a colony of 100 000 macaques. Field studies were conducted in 2006-2007 to harvest biological samples on 20 domestic and wildlife species on Reunion and 5 species on Mayotte. Primates were investigated on Mayotte (brown lemur - *Eulemur fulvus*), on Reunion (monkeys from St-Denis zoo) and on Mauritius (crab-eating macaque - *Macaca fascicularis*). Blood was also collected from animals suspected of CHIK infection by veterinarians and on animals belonging to infected patients. Over 1,500 and 2,000 animals were sampled in 2006 and 2007. In 2006, 807 sera were analyzed by qRT-PCR for viral RNA detection but were negative. To date, sera are screened for neutralizing antibodies using a standard seroneutralization assay and by an ELISA test. Observed seroprevalences greatly vary between species. First results raise the questions of vector tropism, CHIK virus diversity, and epidemiological implications for the CHIK virus transmission in the Indian Ocean, but confirm that the CHIK transmission cycle was mainly a human-mosquito-human cycle.

Epidemiology of infection and disease

Rapid method – A rapid seroprevalence survey involved 900 pregnant women in Reunion who had a blood sample taken between January 15, and February 15, 2006, from a sera toxoplasma collection, indicated that 18% were seropositive for CHIK. It suggested that 140,000 persons had been infected and that more than 80% of Reunion population remained at risk for CHIK as the surveillance data estimated that 157,000 persons consulted a doctor for clinical CHIK. In Mayotte, a rapid serologic survey, carried out from two sera toxoplasma collections based on a similar methodology (12) led to a drastic revision of the 5% seroprevalence estimate based on public health surveillance, as the seroprevalence rate among pregnant women had grown from 0 to 24 % between November 2005 and March 2006, and was at that period similar to that seen in Reunion (24%).

Academic method – A seroprevalence survey based on a representative sample of Reunion population took place after the epidemic wave between August and October 2006 (25). This was a cross-sectional survey based on probabilistic sampling with two degrees: randomization of 3032 households after stratification for the size of the community and the type of residence; and random selection, by the investigator, of one person among those living in the household. A drop of blood was put on filter paper and individual questionnaires and observation forms describing the habitat were completed. Finally, data on 2,442 index subjects were used. The prevalence of CHIK in Reunion was thus 38.25% (CI 35.9-40.6). Six per cent of seronegative persons spontaneously declared a history of CHIK and 6% of seropositive persons failed to spontaneously declare a history of CHIK. The seroprevalence rate differed according to localization ($P < 0.0001$: North 29.6%, South 38.0%, West 41.4%, East 48.0%), and according to the type of household ($P < 0.0001$: collective 23.1% (95%CI [19.4-27.3]), individual 42.9% (95%CI [40.1-45.7]). The seroprevalence was similar in men and women but differed with age ($P < 0.0001$), as follows: 0-9 years: 26.8%, 10-19 years: 42.0%, 20-29 years: 33.7%, 30-39 years: 38.0%, 40-49 years: 38.9%, 50-59 years: 42.9%, 60-69 years: 49.9%, 70-79 years: 61.9%, 80-89 years:

Table 1. Main factors correlated to chikungunya infection (percentage of explained variance)

Factors	*1*	*2*	*3*	*4*	*5*
Percentage of explained variance	**35.00**	**11.99**	**9.11**	**6.59**	**5.70**
CHIKV: positive	**-0,194**	*-0,075*	*-0,137*	*-0,076*	*0,054*
CHIKV: negative	**0,138**	0,054	0,096	0,055	-0,040
Occupation: Bleu-collar or manual workers	**-0,296**	*0,140*	*-0,083*	*-0,396*	*-0,241*
Occupation: Other	0,050	-0,024	0,013	0,068	0,041
Residence: Urban	*0,167*	**0,332**	*0,266*	*0,018*	*-0,084*
Residence: Rural	-0,040	**-0,079**	-0,064	-0,004	0,020
CHIKV is only transmitted by Mosquitoes: Agree	**0,112**	*-0,034*	*0,002*	*-0,059*	*0,034*
CHIKV is only transmitted by Mosquitoes: Disagree	**-0,392**	0,121	-0,010	0,208	-0,123
CHIKV is in the air: Agree	**-0,174**	*-0,059*	*0,008*	*0,098*	*-0,162*
CHIKV is in the air: Disagree	0,085	0,028	-0,005	-0,047	0,081
CHIKD is contagious: Agree	**-0,377**	*0,041*	*0,022*	*0,094*	*-0,079*
CHIKD is contagious: Disagree	**0,203**	-0,022	-0,012	-0,051	0,045
CHIKD can be controlled: Agree	*0,072*	*-0,026*	*0,060*	*-0,029*	*-0,059*
CHIKD can be controlled: Disagree	**-0,215**	0,076	-0,180	0,087	0,174
Protections are useless: Agree	**-0,264**	*0,116*	*-0,137*	*0,178*	*0,083*
Protections are useless: Disagree	0,089	-0,039	0,047	-0,06	-0,027
CHIKV was brought by tsunami: Agree	**-0,363**	*-0,051*	*0,177*	*-0,041*	*0,104*
CHIKV was brought by tsunami: Disagree	**0,166**	0,024	-0,079	0,018	-0,047
CHIKV was introduced by spies: Agree	**-0,388**	*-0,042*	*0,154*	*-0,018*	*0,091*
CHIKV was introduced by spies: Disagree	0,129	0,014	-0,051	0,006	-0,030
CHIKV was brought by a crew: Agree	*-0,155*	*-0,043*	*0,115*	*-0,046*	*0,059*
CHIKV was brought by a crew : Disagree	0,218	0,060	-0,160	0,065	-0,086
Education: > High School	**0,257**	*-0,027*	*0,035*	*0,088*	*0,083*
Education: < High School	**-0,204**	0,021	-0,028	-0,07	-0,065
Use of repulsive means: occasional or frequent	0,064	**-0,113**	0,082	0,042	-0,019
Use of repulsive means: None	-0,125	**0,221**	-0,158	-0,082	0,039
Use of insecticide sprays: None	0,057	**0,259**	-0,014	-0,047	0,078
Use of insecticide sprays: occasional or frequent	-0,027	**-0,125**	0,007	0,020	-0,039
Use of prophylactic means: None	0,042	**0,320**	0,149	0,009	0,034
Use of prophylactic means: occasional or frequent	-0,016	**-0,117**	-0,055	-0,004	-0,013

45.5%, 90+: 54.2%. A similar survey conducted in November 2006 in Mayotte showed 38.1% (CI 35.2-41.0) seroprevalence and confirmed that many cases had gone unreported.

The role of social science in arboviroses outbreaks

In April 2006, a research was launched in Reunion in order to identify the relationships between sociodemographic variables, the perception of the risk of infection, the subjective experience of the disease, and the beliefs and behaviors of the exposed population. The main results are listed in the table 1. They show that manual workers had a 1.97-fold higher risk of infection and that the risk fell by 25% for each step on the socioprofessional scale used (odds ratio 0.74). Above all, living in a detached house with a garden multiplied the risk by 3.68. The sociodemographic profile of a Reunion Island inhabitant "at risk" in 2006 was that classically seen during infectious epidemics, namely a person belonging to the poorest social category, and also one living in a small house with a garden. This study showed that the most effective preventive means were repellent sprays and creams. Thus, 36% of respondents who said they often used these means of protection had been infected by the virus, versus 48% of those who said never used them ($p = 0.002$). None of the other means of protection had a measurable impact on the risk of infection. Moreover, alternative beliefs on the origin or transmission of CHIK were significantly associated with the prevalence of the infection and directly linked to a lack of protection.

A survey was conducted in Mayotte between December 1st, 2006 and January 10, 2007.

In the 420 households, 888 people aged over 14 years of age were tested for antibodies to CHIK and dengue viruses: 38.6% said they had contracted CHIK; 81.4% of these self-reports were serologically confirmed; 24.2% of respondents who thought they were infected were seronegative for CHIK or for dengue fever; 14.9% of respondents who thought they were not infected were seropositive for CHIK, and could be considered as asymptomatic infections. Seventy-seven per cent of respondents thought transmission occurred via mosquito bites, 64% by blood transfusion, 40% by sexual intercourse, 30% via animals, and 21% by shaking the hand of an infected person.

Cost of chikungunya disease in Reunion

Tourism in Reunion that represents 360 million euros was particularly hard-hit. Reunion lost 130,000 tourist visitors during the crisis, causing a lost of 110 million euros. Gross National Product was eventually impacted of 88.6 million euro, due to partial compensation from local activity. The highest impacted sectors were hotels and restaurants (-10.2%), services (-2%), food industry, market activity, finance activity, and fishing (between -1.0% and -1.5%). The epidemic could thus serve as a model for studying the impact of a major epidemic in a modern country.

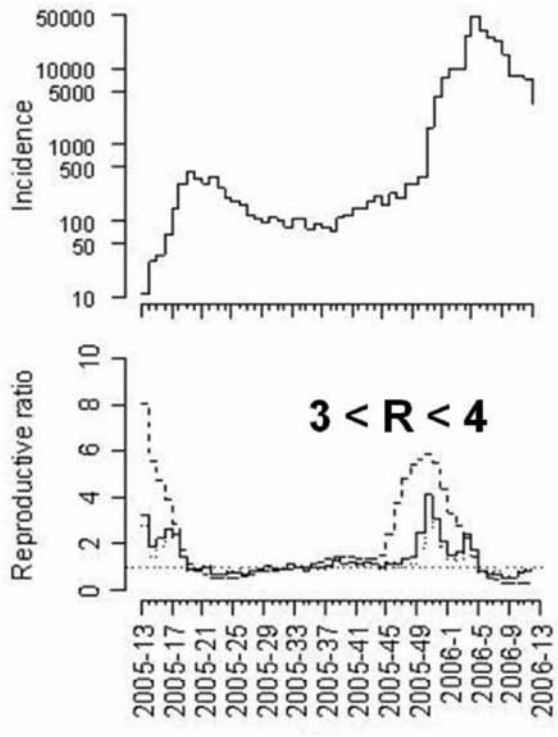

Figure 2. Incidence (upper graph, note the logarithmic scale on the X axis) and reproduction rate (lower graph) of the chikungunya epidemic, Reunion Island 2005-2006, based on data published by InVS and the Reunion Island CIRE.

The concept of "health meteorology": mathematical modeling to predict epidemic trends

In epidemiology, a theorem is used to define an epidemic threshold, when the baseline level of reproduction (R0) exceeds 1. R0 corresponds to the number of secondary cases generated by an index case in a fully susceptible population (26). The proportion (Pi) of individuals who must be immunized in order to avoid the risk of epidemic resurgence is Pi = 1 – 1/R0. We adapted newly developed epidemiological tools to vector-borne diseases. The transmission potential was measured by the number of secondary cases per index case R estimated weekly from the chronological series of the first 12 months (Figure 2). It showed that despite massive difference in magnitude between the first two epidemic waves - 3000 cases in a first wave (March to June 2005), 266,000 cases in a second (December 2005 to April 2006) – R remained similar in the two consecutive waves. The best estimate for the initial reproduction number R0 was 3.7, with a possible range from 2 to 11 (27). Therefore, an increase in virulence between the two seasons was not necessary to explain the change in magnitude of the epidemics. However, on September 2007, no epidemic resurgence had been recorded in Reunion with an attack rate remaining below 40%, despite sporadic circulation of chikungunya virus. The lack of resurgence may well have been due to collective and individual vector control measures, and especially to effective use of repellents and destruction of domestic and peridomestic larval shelters by the population and authorities. It is also possible that attack rate in Reunion masks a certain heterogeneity, with very high rates of acquired seroprotection in places where the inhabitants were most vulnerable in 2005 and 2006.

Sensitivity to insecticides and assessment of the environmental impact of vector control measures

The sensitivity to *Ae. albopictus* to insecticides used in 2006 in Reunion, deltamethrine and *Bacillus thuringiensis israelensis*, was assessed according to standard WHO protocols. All eight tested strains originated from different geographical location in Reunion Island, were sensitive to both insecticides at usual doses. A comparative assessment of the efficacy and environmental and health risks of using deltamethrine and fenitrothion to kill adult mosquitoes was also conducted.

Assessment of new candidate insecticides and new strategies to control mosquito arbovirus vectors – As the number of chemicals available for killing mosquitoes is dramatically small, French government is supporting phase 1 and phase 2 studies on new insecticides efficient against *Aedes* mosquitoes. Two larvicides (pyriproxyphen and spinosad) and 2 adulticides (naled and pyrethrum) are being tested against sensitive and insecticides resistant populations of *Ae. aegypti* in Martinique. A preparatory research programme for the control of *Ae. albopictus* and *Anopheles arabiensis* from Reunion using the Sterile Insect Technique (SIT) is under investigation.

Perception and acceptability of risks linked to the use of pesticides against mosquito vectors of chikungunya virus in Reunion Island - The short-term impact of insecticides on vertebrates and non target invertebrates has been assessed. Insecticides did not have any major immediate impact on the environment and on aquatic and terrestrial fauna, but long-term effects are unknown.

Conclusions

In the field of the recent outbreak of chikungunya in the French overseas territories, a task force composed by scientists belonging to the main relevant domains has proven its efficacy in understanding and finally mastering the phenomenon. Within a very short span of time, it has conceived and proposed needed researches to increase understanding of the disease and of the epidemic and to perform and / or trigger collaborative research programs to enlighten health authorities in their response. It has also pointed where knowledge is still lacking and has created a research centre in Reunion in collaboration with neighboring countries.

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