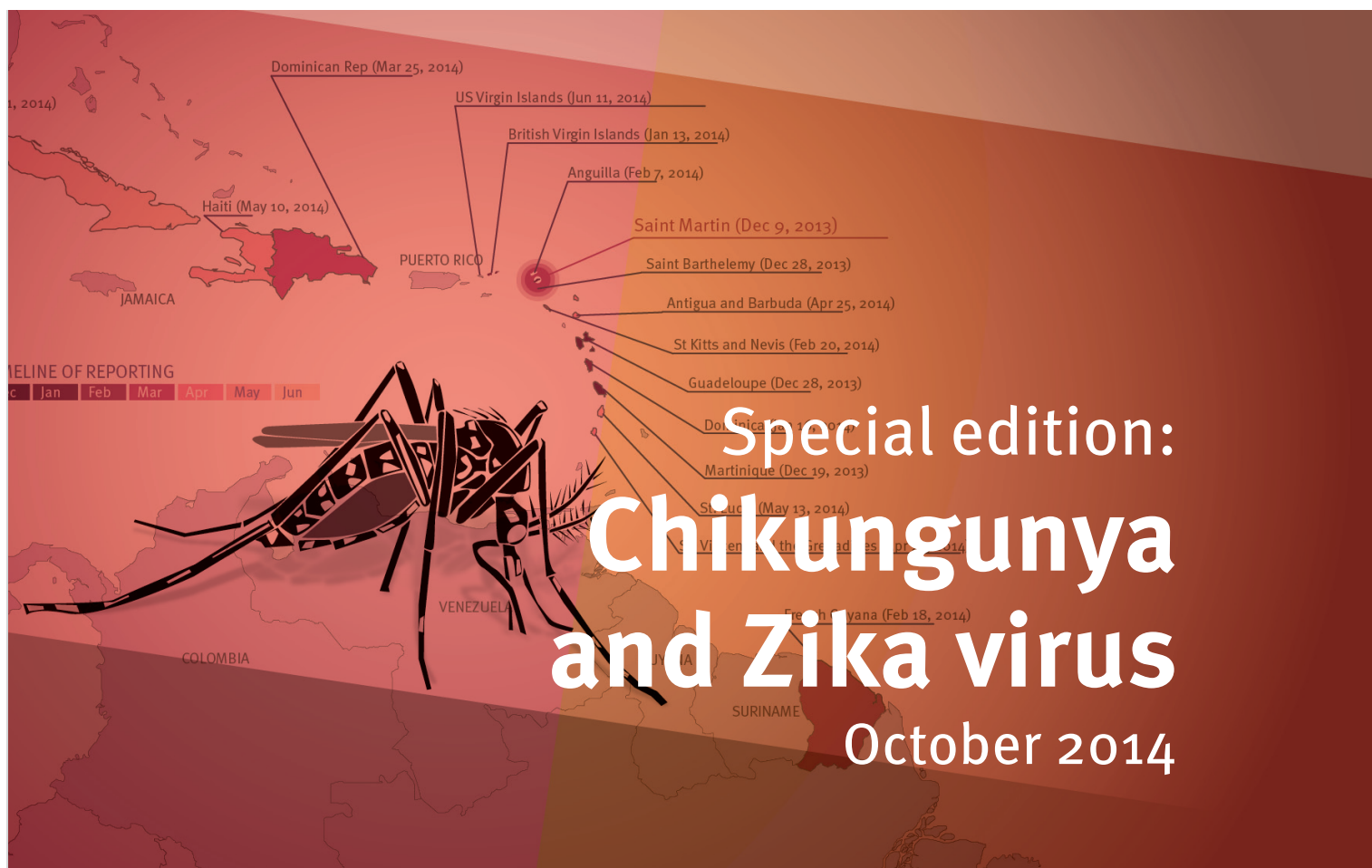




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- Spread of chikungunya from the Caribbean to mainland Central and South America: a greater risk of spillover in Europe?
- Aspects of Zika virus transmission
- Cases of chikungunya virus infection in travellers returning to Spain from Haiti or Dominican Republic, April-June 2014



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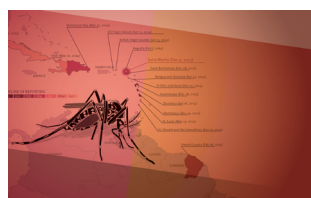
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Illustration of mosquito, map of outbreak

Integrated surveillance for prevention and control of emerging vector-borne diseases in Europe

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World Health Day, celebrated on 7 April, marks the anniversary of the founding of the World Health Organization (WHO) in 1948. This year, vector-borne diseases which are transmitted mainly by bites of vectors such as mosquitoes, ticks and sandflies are highlighted as a global public health priority. This issue of *Eurosurveillance* focuses on vector-borne diseases and their impact on public health in Europe and other parts of the world such as the recent outbreaks of Chikungunya fever in the Caribbean and Zika virus fever in the Pacific [1-6].

Mosquito-borne diseases

Dengue and malaria are important mosquito-borne viral diseases, often also referred to as ‘tropical’ diseases. Globally, dengue is the most common mosquito-borne viral disease, with an estimated 390 million infections per year and 40% of the world’s population at risk [7]. While interventions to control mosquitoes have resulted in a decrease of malaria cases, WHO nonetheless estimates that 219 million individuals were infected in 2010, of which 660,000 died, predominantly in Africa [8].

Yet, vector-borne diseases are also a threat to public health in Europe. Mounting an effective public health response can counteract challenges posed by them and protect humans from infections; dedicated activities such as disease and vector surveillance as well as monitoring infectious disease drivers (e.g. environmental or climatic conditions) can help to anticipate and to respond to emerging vector-borne diseases [9, 10].

Globalisation and environmental change; social and demographic change; and health system capacity are three interacting drivers that can set the stage for novel vector-borne disease scenarios [11]. The changing dynamic of these drivers can potentially create new constellations of threats that challenge control measures. Pathogens and vectors are bound to disseminate rapidly through globalised transportation networks: over 100 million air travellers alone enter continental Europe annually, connecting it to international ‘hot

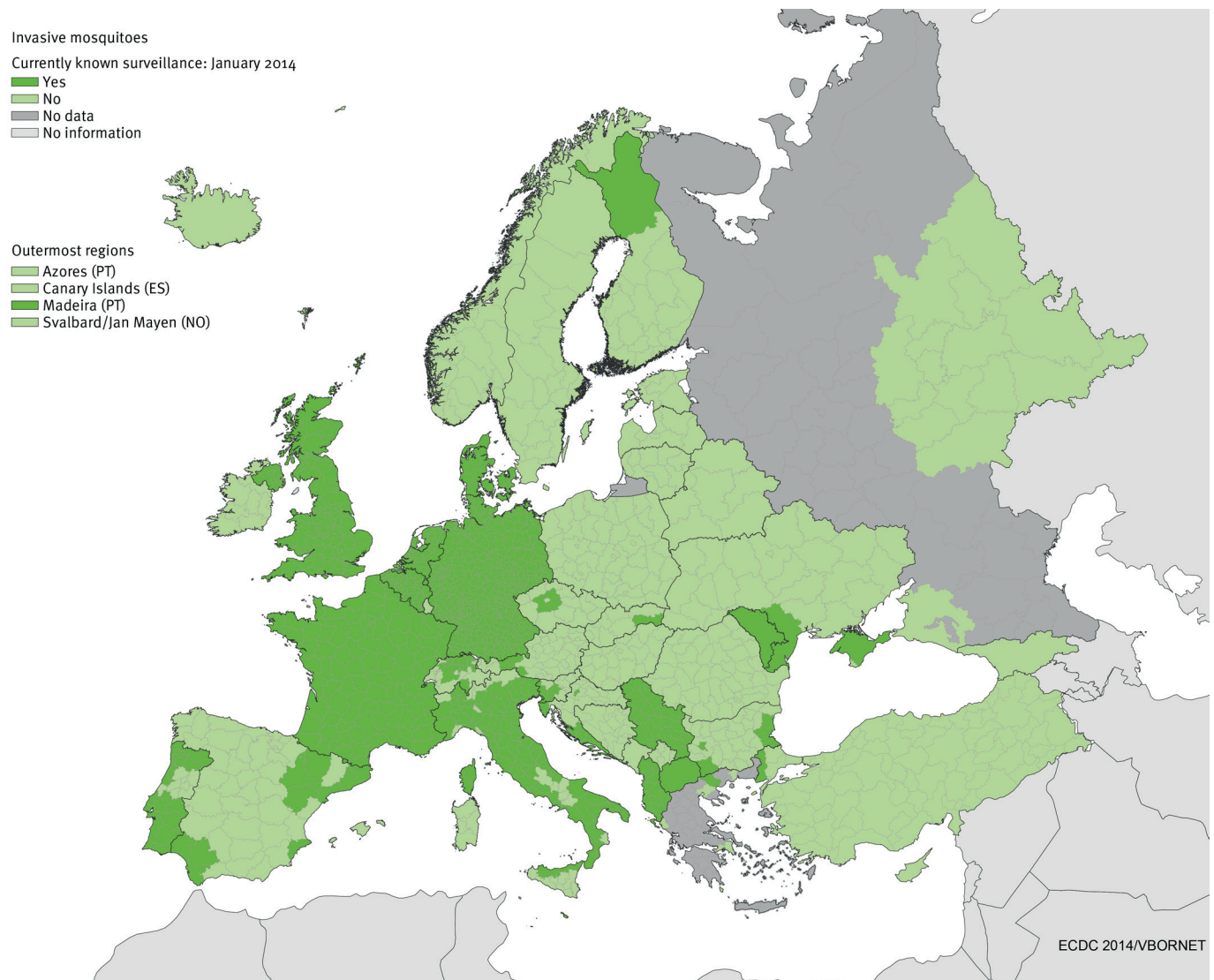
spots’ of emerging infectious diseases [12]. A case-in-point is the importation, establishment and expansion of the Asian tiger mosquito (*Aedes albopictus*), first recorded in Albania in the 1970s and subsequently in Italy in the 1990s. The mosquito was imported in used car tires from the United States into Genova and Venice, both in Italy, from where the mosquito spread [13]. Dedicated vector surveillance activities (Figure 1) have documented that the vector has expanded due to permissive climatic and environmental conditions and is now established in numerous regions in Europe.

Astute surveillance activities were able to detect the autochthonous transmission of Chikungunya and dengue viruses by *Ae. albopictus* in Europe triggered by infected travellers returning from endemic areas [13, 14]. Through vector surveillance, *Ae. aegypti* mosquitoes, the main vectors of dengue, were first detected in Madeira, Portugal in 2005 where they dispersed across the southern coastal areas of the island. From September 2012 to January 2013, the island experienced a large dengue outbreak, affecting more than 2,100 individuals, including 78 cases exported to continental Europe; the responsible dengue virus serotype DEN-1 was traced back to a probable Central or South American origin [15].

In December 2013, public health surveillance confirmed the first local transmission of Chikungunya virus in the Caribbean. Within three months the virus spread from Saint Martin island to six other neighbouring islands and autochthonous transmission was even reported in French Guiana, South America. Cassadou et al. and Omarjee et al. in this issue describe the importance of proactive public health practice during such a vector-borne disease emergence [1]. Chikungunya infections were identified in a cluster of patients suffering from a febrile dengue-like illness with severe joint pain and who tested negative for dengue. The outbreak illustrates the importance of a preparedness plan with awareness of healthcare providers, adequate laboratory support for early pathogen identification, and

FIGURE

Currently known vector surveillance activities in Europe, January 2014



The surveillance activities include not only specific surveillance studies but also work done as part of on-going control activities, research projects and inventory studies.

Source: European Center for Disease Prevention and Control, 2014 [25].

appropriate response. Incidentally, in the past, several imported cases of Chikungunya fever were reported but did not result in local transmission or spread to surrounding islands.

Zika virus, transmitted by *Ae. aegypti* mosquitoes and originated from Africa and Asia emerged in French Polynesia in September 2013 and posed another health threat by *Ae. albopictus* mosquitoes [16]. In this issue, Musso et al. report the first evidence of perinatal transmission of the Zika virus [2].

The parasitic mosquito-borne disease malaria was once common mainly in southern parts of Europe. While it had been eliminated largely via sanitary measures, local transmission has sporadically returned to Europe in recent years and cases from endemic

countries continue to be routinely imported into Europe via travelers. In Greece, malaria had been eliminated in 1974 but starting in summer 2009 through 2012, locally acquired cases of *Plasmodium vivax* occurred in the summer months, mostly due to multiple re-introductions of the parasite [14]. The continuous spread of *P. vivax* by local anopheline mosquitoes raised the possibility of a sustained malaria transmission. In order to guide malaria control, areas with suitable environments for persistent transmission cycles were identified through multivariate modelling of environmental variables [17]. With information about this environmental fingerprint and using European Union (EU) structural funds, adequate measures could be taken and transmission in these areas was interrupted. Targeted epidemiological and entomological surveillance, vector abatement activities, and awareness raising among the

general public and health workers proved to be successful to this effect.

A further important viral vector-borne disease is West Nile fever (WNF). It was first recognised in Europe in the 1950s and re-emerged in Bucharest in 1996 and Volgograd in 1999 [13, 14]. Since then, several countries experienced limited outbreaks until 2010, when Europe witnessed an unprecedented upsurge in the numbers of WNF cases [18]. Ambient temperature deviations from a thirty year average during the summer months correlated with a WNF outbreak of over 1,000 cases in newly affected areas of south-eastern Europe [19]. Since the emergence of WNF in Greece in 2010, the disease has spread in the country reaching both rural and urban areas. In the subsequent summers from 2011 to 2013, the outbreaks did not subside in these areas. An article by Pervanidou et al. in the current issue describes the third consecutive year of autochthonous West Nile virus transmission in Greece [3]. It is a descriptive analysis of the 2012 outbreak, confirming risk factors such as advanced age, for severity of disease and medical risk factors such as chronic renal disease, for mortality from WNF.

Temperature determines viral replication rates, growth rates of vector populations and the timing between blood meals, thereby accelerating disease transmission [18]. With global climate change on the horizon, rising temperatures might be a climatic determinant of future WNV transmission that can be used as an early warning signal for vector abatement and public health interventions [13].

Tick-borne diseases

Tick-borne diseases are also of public health concern in Europe. Tick-borne encephalitis (TBE) is endemic in Europe and due to its medical significance was recently added to the list of notifiable diseases with a harmonised case definition focussing on neuroinvasive illness with laboratory confirmation [20]. The main vector of TBE, *Ixodes ricinus*, is widely distributed in Europe while TBE virus transmission is restricted to specific foci. Integrated surveillance is important to precisely determine these locations of active transmission to humans to better assess the risk and inform the public about adequate preventive measures which include protective clothing as well as vaccination. Schuler et al. in this issue describe the epidemiological situation of TBE in Switzerland over a five year period, showing the heterogeneity of the incidence according to cantons and the importance of the surveillance and vaccination as a preventive measure [4].

Tick activity is determined by ecological environmental conditions [21]. TBE incidence has been affected by both climatic and socio-demographic factors [13]. The political changes in the 1990s after the dissolution of the former Soviet Union, might have contributed to the transmission of TBEV in the Baltic countries (Estonia, Latvia and Lithuania) and in eastern Europe

by increasing the vulnerabilities for some population subgroups. A case control study from Poland found that spending extended periods of time in forests harvesting forest foods such as mushrooms, being unemployed or employed as a forester significantly increased the risk for TBE infections [22]. In central Europe, climate change-related temperature rise has been linked to an expansion of TBE virus transmitting ticks into higher altitude [23].

Lyme borreliosis, another endemic tick-borne disease, is believed to be the vector-borne disease with the highest burden in Europe. Climate change may be affecting the risk of Lyme borreliosis in Europe [13]; it has already been demonstrated that *Borrelia* transmitting ticks have been associated with an expansion into higher latitudes in Sweden [24].

Collectively, these examples demonstrate that vector-borne diseases remain an important challenge to public health in Europe. Monitoring environmental and climatic precursors of vector-borne diseases linked to integrated surveillance of human cases and vectors can help counteract potential impacts [9, 10]. Certainly, raising awareness and increasing knowledge among the general public, public health practitioners, and policy makers about disease vectors and their relationship with infectious diseases remains a priority also. Exposure prevention through personal protection and vector abatement are important components of effective intervention strategies. In addition, integrated vector surveillance of invasive and endemic mosquito species is crucial for effective prevention and control of vector-borne diseases.

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Spread of chikungunya from the Caribbean to mainland Central and South America: a greater risk of spillover in Europe?

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After a decade of outbreaks in Africa, the Indian Ocean and Asia, chikungunya virus (CHIKV) is stepping out of the shadow of dengue virus [1]. Although these two mosquito-borne viruses share clinical characteristics and their main vectors, *Aedes albopictus* (the tiger mosquito) and *Ae. aegypti*, CHIKV has long remained exotic to the western hemisphere [2]. The emergence of the Indian Ocean lineage changed the views on CHIKV when it caused an unprecedented disease burden in India and the islands of the Indian Ocean between 2005 and 2008 [3,4].

More than the reports of single events of locally-acquired cases of chikungunya fever in Italy and France [5,6], the recent occurrence of autochthonous transmission of CHIKV in the Americas has redesigned the geographic distribution of the virus. An outbreak in the Caribbean caused by an Asian strain of the virus started in Saint Martin in October 2013 with *Ae. aegypti* as the primary vector. The dynamics of the spread of CHIKV was in line with that in outbreaks that occurred in the Indian Ocean [2].

In this issue of *Eurosurveillance*, Cauchemez et al. estimate the basic reproductive number (the mean number of new host cases generated by one infectious host in a completely susceptible human population) at between 2 and 4 in the initial phase of the outbreak in the French Caribbean [7]. This is close to estimates from the outbreaks in Italy in 2007 and on Réunion Island in 2006 (3.5 and 3.7, respectively) [8,9].

Data from epidemiological surveillance suggest that so far, six months after its introduction to the Caribbean, CHIKV has been responsible for over 350,000 suspected cases of chikungunya fever that have occurred throughout the region [10].

The consequences of the outbreaks in the Caribbean have ripples in Europe, as Paty et al. and

Requena-Méndez et al. document in this issue [11,12]. Paty et al. report the increased detection through surveillance of infected travellers arriving in mainland France from the French West Indies [11]. Likewise, the importation of chikungunya cases presented by Requena-Méndez et al. in this issue are likely to continue for months in Spain and other countries with intense exchanges with South America [12]. Cauchemez et al. stress that if circulation of CHIKV settles in mainland South and Central America, the international spillover of cases could escalate [7]. At this moment, public health surveillance has already detected local transmission of CHIKV on the continent, in Costa Rica, Guyana, El Salvador, Suriname and French Guiana [10].

Based on the recent rapid risk assessment from the European Centre for Disease Prevention and Control (ECDC), the chikungunya epidemic in the Americas represents a tangible threat to public health in Europe that goes beyond the scope of travellers' health [13]. In this globalised world, it could ignite local diffusion of CHIKV in Madeira that is colonised by *Ae. aegypti* and in the constantly expanding areas in Europe where *Ae. albopictus* is established. Vector competence studies are ongoing, but it is highly likely that *Ae. albopictus* will be found competent for transmission of the CHIKV strain circulating in the Caribbean. Local tiger mosquitoes were able to transmit CHIKV strains of the Indian Ocean lineage to more than 250 cases in Italy in 2007 and to two cases in France in 2010 [5,6].

Local foci or even large outbreaks are more likely to occur in Europe now because of the synchronicity between CHIKV transmission on the other side of the Atlantic and the season of vector activity in Europe. Preventing the spillover of the chikungunya outbreak to Europe in this challenging context requires the mobilisation of the population and cross-sector collaboration between clinicians, medical biologists, entomologists

and public health professionals at local, national and European level in as part of the One Health concept.

The odds of controlling CHIKV dissemination to Europe will become lower if, as expected, CHIKV spreads during the summer to continental South America. Indeed, it is plausible that the long feared epidemic in South America will be ongoing for months and maybe years, continuously fuelling the flow of imported cases.

There are no prospects of a human vaccine or curative antiviral treatment available in a near future. Therefore, the only opportunity of preventing dissemination to Europe consists in reducing the vector density and its contacts with humans. People living in an area colonised by *Aedes* vector mosquitoes should be taught how to prevent and eliminate man-made breeding sites to reduce the overall vector density around their homes and workplaces. They should be informed about personal protective measures to avoid mosquito bites such as wearing long-sleeve shirts and long trousers and using repellent on exposed skin. Travellers should strictly observe the recommendations for personal protection against mosquito bites while visiting areas where CHIKV transmission is active. In case of fever upon return to an area where the vector is established, travellers should seek medical attention and prevent mosquito bites while symptomatic. Because both vector mosquitoes are day biters, nets are of limited use. But they can be useful to protect in particular young children and infected patients that are resting. Healthcare professionals should become increasingly aware of the clinical presentation and diagnostics of chikungunya, as well as treatment relieving symptoms. They should advise travellers and cases about protective measures against mosquitoes.

Vector control measures should target both adult mosquitoes and larvae and rely on a limited set of insecticides that are active against *Aedes* spp. These insecticides should be used sparingly and only for targeted responses so as to avoid toxic effects on humans and the surrounding fauna as well as the emergence of resistant insects. For this reason, implementing surveillance systems for local entomological indicators in Europe is crucial in order to estimate the risk of local transmission associated with imported cases and to guide vector control measures in time and space.

Thus, it is crucial to be prepared. European Union (EU) Member States are advised to develop preparedness planning for identifying new health threats at national level according to the recent *Decision 1082/2013/EU* on serious cross-border threats to health [14]. The CHIKV control measures at EU level require: entomological surveillance, surveillance of imported and autochthonous cases and rapid diagnosis to detect local outbreaks. Moreover, vector control measures should be included in the planning around cases, either after rapid diagnosis or, in patients returning from epidemic

areas, without waiting for laboratory confirmation results.

However, underreporting of cases can be substantial. Published reports suggest that the estimated number of imported cases generally exceeds the number of notified cases by a factor 10 and over [15,16]. Active mobilisation of clinicians and medical biologists in targeted geographical areas has proven efficient to improve completeness of the surveillance of dengue virus and captured up to 69% of cases [16].

At this stage, surveillance should be based primarily on laboratory confirmation. At EU level, new case definitions for dengue and chikungunya fever are being developed, based on the group discussion that took place during the meeting of ECDC Emerging and Vector-borne Diseases (EVD) network in December 2013 [17]. A case definition including only epidemiological and clinical criteria should be considered to monitor large outbreaks when systematic laboratory confirmation is not feasible any more.

The threat that the chikungunya outbreak in the western hemisphere represents for public health in Europe, should not overshadow the risk posed by other arboviruses such as dengue virus. Globalisation and environmental changes affect the dynamics of both viruses in Europe in the same way. Recent reports of limited autochthonous transmission of dengue virus and large-scale outbreaks in Europe call for continued vigilance and involvement [18-20]. When confronted with a febrile patient returning from tropical and subtropical areas, practitioners should now consider both diagnoses. Both mosquito-borne viral diseases can be tackled by the same surveillance and response efforts.

Laboratory capacity for CHIKV infections in the EU is limited and should be increased for early detection of cases. In 2007, the European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD) conducted an external quality assurance survey of serological and molecular methods used for CHIKV detection [21]. That study unveiled great differences in the availability and performance of CHIKV diagnostics among the 24 participating laboratories from 15 countries across Europe. There is little available information to make us believe that the situation since has notably improved. Most of these laboratories are still using in-house techniques and may not be able to cope with a considerable increase in activity. New and reliable commercial serological and molecular tests are needed to improve access to CHIKV diagnostics in Europe.

CHIKV also represents a threat for blood safety in Europe. The recent detection of CHIKV among blood donors from Guadeloupe and Martinique in early 2014 alerts us to the risk of transfusion-transmitted infections [22]. Temporary deferral of donors returning from areas of active transmission of CHIKV is an effective way of preventing transfusion-transmitted infections.

In case of local transmission of CHIKV in the EU, different measures should be considered according to the intensity of vector-borne transmission in the community. These measures include discontinuing blood collection in affected areas, screening donors for symptoms, post-donation quarantine and CHIKV RNA detection in donations.

In summary, the introduction of chikungunya in the Caribbean and the Americas illustrates how quickly diseases can spread with international travel. In the coming months, chikungunya cases among travellers visiting or returning to Europe are likely to increase. European public health authorities should therefore not underestimate the transmission potential of CHIKV and should remain vigilant. These imported cases could trigger local outbreaks in Europe where the competent vector is established. Levels of risk and preparedness appear very heterogeneous between and within countries. We believe that ECDC can lend support to EU Member States in preparing for potential local chikungunya outbreaks by building capacity and strengthening networks in collaboration with international stakeholders in this global event.

Conflict of interest

None declared.

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Dengue virus serotype 4 and chikungunya virus coinfection in a traveller returning from Luanda, Angola, January 2014

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A concurrent dengue virus serotype 4 and chikungunya virus infection was detected in a woman in her early 50s returning to Portugal from Luanda, Angola, in January 2014. The clinical, laboratory and molecular findings, involving phylogenetic analyses of partial viral genomic sequences amplified by RT-PCR, are described. Although the circulation of both dengue and chikungunya viruses in Angola has been previously reported, to our knowledge this is the first time coinfection with both viruses has been detected there.

Detection of coinfection

Here we report the simultaneous detection of chikungunya virus (CHIKV) and dengue virus (DENV) genomes in the peripheral blood of a traveller who returned from Luanda, Angola, to Portugal in January 2014.

The traveller, a woman in her early 50s, was born and raised in Angola and has lived in Lisbon, Portugal, since the early 1990s. She stayed in Luanda from mid-December 2013 to early January 2014 at her family's place of residence. There were a large number of mosquitoes in the garden and the patient was repeatedly bitten during her stay.

The patient reported feeling unwell in early January, two days before her return to Portugal. Her condition worsened during the flight, and in the next few days she had high fever (up to 39.5 °C), severe arthralgia, myalgia, prostration and abdominal pain. Three days after her return, she went to the emergency department of a hospital: a malaria blood smear was negative and among a range of laboratory tests (including coagulation speed and levels of glucose, creatinine, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), sodium, potassium, chloride ions and C-reactive protein), the only

abnormal findings were a mildly low platelet count ($139 \times 10^9/L$; norm: $150\text{--}400 \times 10^9/L$) and mild leucopenia ($2.9 \times 10^9/L$; norm: $4\text{--}10 \times 10^9/L$). The following day, she went to a hospital specialised in tropical diseases, where photophobia was detected. Further tests were carried out (described below). An arbovirus infection was suspected as the malaria blood smear was persistently negative.

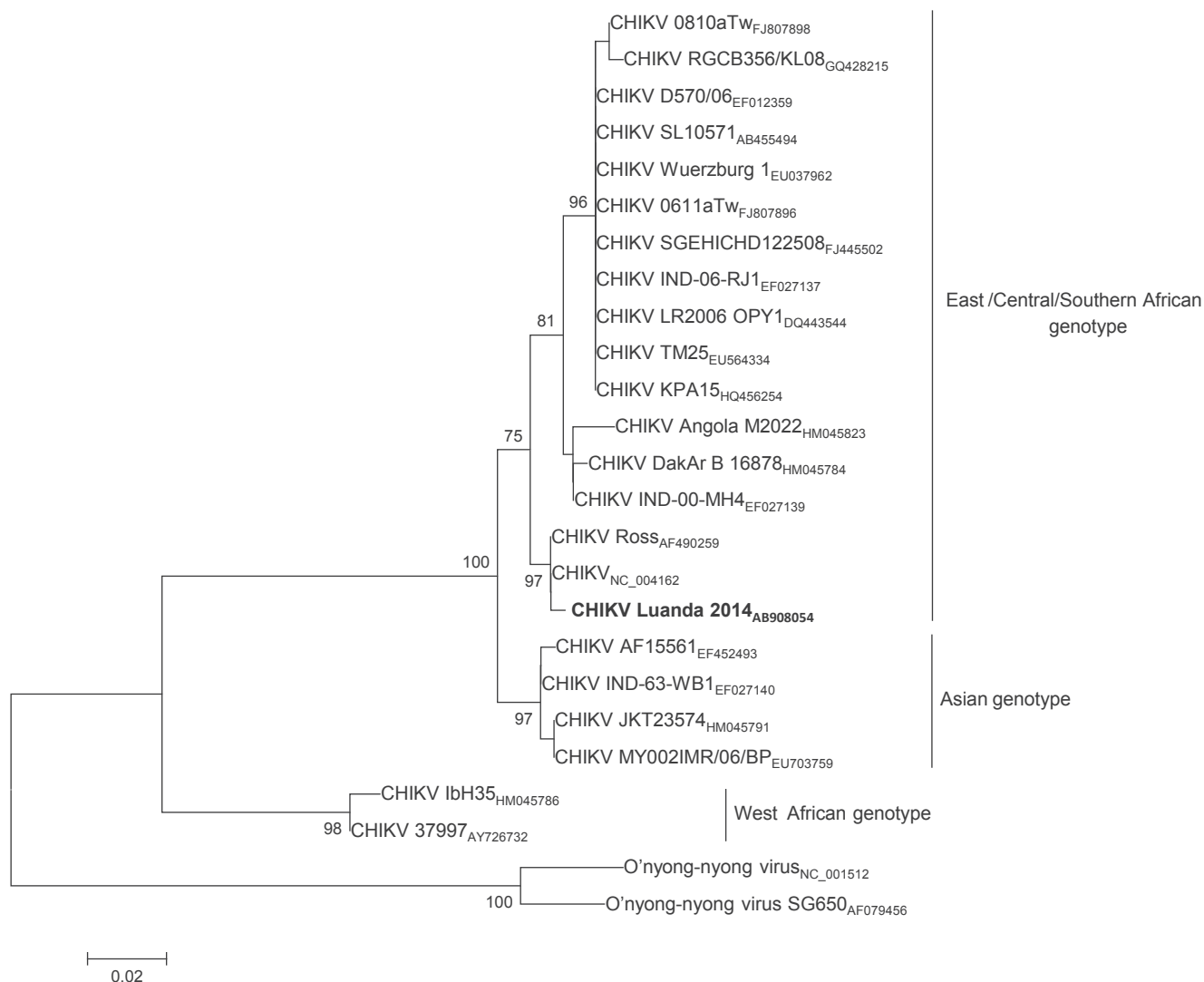
Four days later, the fever had subsided and her condition improved progressively over the next two to three weeks. The patient did not have a rash, conjunctivitis or other clinical signs of a complicated dengue infection (DENV infection with haemorrhage); indeed, she had no other abnormal clinical signs at all during the course of her illness. To the best of her knowledge, none of her family or neighbours in Luanda experienced a similar illness.

Laboratory findings

Four days after her return from Luanda, DENV nonstructural (NS) protein 1 and anti-CHIKV IgM were detected (through the use of SD BIOLINE Dengue Duo NS1 Ag + Ab Combo and SD Bioline Chikungunya IgM), while DENV-specific IgM and IgG were not detected. Two days later, the same tests were performed: anti-CHIKV IgM and DENV-specific IgM and IgG were detected, but DENV NS1 was not. Using RNA extracted from the blood sample where NS1 had been found, detection of the viral genomes was carried out either by a nested RT-PCR as previously described [1,2] or by using primers that target the virus packaging sequence [3]. The sizes of the amplicons obtained were compatible with the presence of both DENV4 (approximately 390 bp, covering the C-prM region) and CHIKV (approximately 350 bp, in the NS2 coding region).

FIGURE 2

Maximum likelihood phylogenetic tree of chikungunya virus (CHIKV) partial nonstructural protein (NS) 2 sequences



The tree was constructed using the GTR+I model [4]. The amplicon isolated from the patient is shown in bold. Reference strains are indicated by strain name and accession number. The three CHIKV genotypes (East/Central/Southern African, West African and Asian) are indicated. The numbers at specific branches indicate bootstrap values (values $\geq 75\%$ are indicated). Two strains of o'nyong nyong virus, the *Alphavirus* most closely related to CHIKV, have been used as an outgroup.

Luanda may indicate the circulation of multiple DENV subtypes in the country.

Although clinical examination of CHIKV/DENV coinfecting patients has not yet allowed the identification of specific or severe symptoms, such observations should be interpreted with caution in view of the limited number of clinical and biological investigations reported. Our findings may add to the recognition of CHIKV/DENV coinfections and suggest that tests to detect the presence of both viruses should be carried out in individuals showing clinical signs of an infection with either CHIKV or DENV.

Conflict of interest

None declared.

Authors' contributions

Ricardo Parreira: molecular analyses and manuscript writing. Ângela Mendes: molecular analyses. Jaime Nina: clinical diagnosis and manuscript writing. Antónia Constantino: clinical diagnosis and manuscript writing. Sónia Centeno-Lima and Daniela Portugal Calisto: laboratory diagnosis and manuscript writing.

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Emergence of chikungunya fever on the French side of Saint Martin island, October to December 2013

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On 18 November 2013, five residents of Saint Martin presented with severe joint pain after an acute episode of dengue-like fever. Epidemiological, laboratory and entomological investigations provided evidence of the first autochthonous transmission of chikungunya virus in the Americas. The event indicates a risk of epidemics in America and Europe through substantial passenger traffic to and from continental France. We describe detection and confirmation of the first six cases and results of the first weeks of surveillance.

On 16 and 18 November 2013, through health event intelligence, separate signals from two sources, a patient and a hospital practitioner, reached Public Health Nurse (PHN) and epidemiologists, respectively. Five residents of a Saint Martin district called Oyster Pond, which straddles the two sides of the island, presented with severe joint pain after an acute episode of dengue-like fever. Following the alerts, two investigations were carried out in Oyster Pond.

Detection and confirmation of the first six cases: health event activity

Epidemiological surveillance and health event activities on Saint Martin before the outbreak

Saint Martin and Sint-Maarten are parts of the same Caribbean island and are, respectively, French and Dutch overseas territories. Epidemiological surveillance and health event intelligence activities on the French side are performed through a network of health professionals including epidemiologists from the French Institute for Public Health Surveillance (Cire), public health nurses (PHN) from the Regional Agency for Health (ARS), hospital and general practitioners, local laboratory and professionals of vector control. This network has been in place for many years to monitor, for example, the epidemiology of dengue fever that is endemo-epidemic in the French West Indies [1].

Investigations following the first signal of the health event

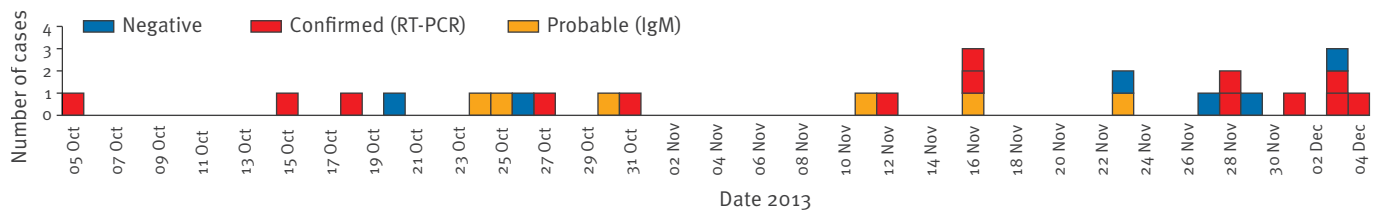
On 21 and 22 November 2013, standardised interviews and an entomological survey were conducted in the Oyster Pond district. In addition to the first five notified patients, three further patients were detected during the investigations in the district and, finally, eight patients were interviewed: five women and three men whose age ranged from 49 to 73 years. Their dates of symptom onset ranged from 15 October to 12 November; fever was acute, with a high temperature ranging from 38.8 to 39.5 °C. Five patients reported rashes (erythema, maculae, papules and, in one case, vesicles). All eight had incapacitating pain, most often in the joints of hands or feet, preventing day-to-day activities. Seven patients also had oedema in the painful joints. Available laboratory data suggested a viral infection because of a normal white cell blood count and a normal level of C-reactive protein, but the specific laboratory tests to confirm dengue fever were negative (IgM and NS1 test) [2-3]. None of the patients reported travelling to countries other than continental France, the Virgin Islands, the United States and Germany, all countries unaffected by chikungunya virus (CHIKV).

A dengue epidemic was ongoing on Saint-Martin at the time, and the vector (*Aedes aegypti*) was present on the island. The entomological investigation following the signal showed a higher density of these mosquitoes in the Oyster Pond district compared with other areas. This observation made a mosquito-borne disease plausible, but the negative laboratory tests suggested a cause other than dengue virus (DENV).

Blood samples of the eight patients were tested in the French National Reference Centre for Arboviruses in Marseille, mainland France. On 2 December 2013, serology results for two cases were positive for CHIKV (IgM). A first positive RT-PCR [4] result for another case was received on 5 December. Overall, six of the eight suspected cases could be laboratory-confirmed: four had positive IgM tests, one had a positive RT-PCR, one

FIGURE

Epidemic curve of chikungunya fever cases by date of symptom onset, Saint Martin, 5 October–4 December 2013 (n=26)



had positive results in both tests. The remaining two patients were negative in both tests. The six confirmed cases were classified as autochthonous, since they had no travel history to countries affected by CHIKV. Diagnostic tests for DENV were negative for all six.

The full-length viral RNA genome was characterised by the French National Reference Centre for Arboviruses, in Marseille. Importantly, the virus did not belong to the East Central South African genotype but to the Asian genotype, phylogenetically related to a number of strains recently identified in Asia (Indonesia 2007, China 2012 and the Philippines 2013) [5].

Detection of later cases

Improvement of surveillance

After the confirmation of virus circulation on Saint Martin, the following four objectives were established for future chikungunya surveillance: detect all new suspected cases in a timely manner, collect epidemiological data, confirm cases by laboratory tests and monitor the spread of the disease on the French side of Saint Martin. Collaboration with the Dutch side of the island was also enhanced with meetings and data exchange, although the preparedness plan did not specifically include such actions.

The definition for a suspected case of chikungunya fever was sent to all hospitals and general practitioners as follows: (i) a patient with onset of acute fever $>38.5^{\circ}\text{C}$ and with at least one of the following symptoms (headache, retro-orbital pain, myalgia, arthralgia, lower back pain) and who had visited an epidemic or endemic area, or (ii) a patient with acute fever $>38.5^{\circ}\text{C}$ and severe arthralgia of hands or feet not explained by another medical condition.

For laboratory confirmation, it was recommended that doctors request simultaneous tests for dengue and CHIKV for all patients fulfilling the case definition. The laboratory in charge of taking blood samples had to fill in a form including the date of symptom onset, date of sample, the address and phone number of the patient. These data were transmitted to epidemiologists and vector control staff. Spatial distribution of the cases

was analysed using the addresses provided for all patients.

As for the first detected cases, all blood samples collected during this second phase of surveillance had to be sent to the National Reference Laboratory in Marseille, France. The laboratory results allowed classification of the clinical suspected cases as follows: invalidated case if all the tests were negative, probable case if only serology (IgM) was positive, confirmed case if RT-PCR was positive, confirmed co-infection if RT-PCR was positive for dengue and CHIKV in the same sample.

Overall results for all 26 suspected cases with laboratory test by 4 December 2013

The epidemic curve (Figure) summarises, by date of symptom onset, the first 26 patients tested between 5 of October and 4 December 2013. These include the first eight patients described above as well as a further 18 suspected cases with available laboratory test. Of those 26, 20 were identified as probable or confirmed cases. Seven probable or confirmed patients were male and 13 were female; the median age was 50 years (range 6–72 years). No patient had to be hospitalised. In addition to these 26 patients, 10 were seen by a doctor who considered that their symptoms fulfilled the criteria of a suspected case, but these patients, probably because of a mild condition, did not go to the laboratory for blood sample taking.

The period of approximately two weeks between the first confirmed case and the subsequent two confirmed cases is consistent with the time required for the contamination of a mosquito, the extrinsic cycle of the virus in this mosquito, the stinging of another patient by this infected mosquito and the incubation period in the new patient. This temporal pattern was repeated for the later groups of probable and confirmed cases occurring in November 2013.

Discussion and conclusion

Epidemiological, laboratory and entomological investigations of the first cases provided evidence for the first active transmission of CHIKV in the Americas.

At the time of the investigations, information available about the international epidemiological situation of chikungunya fever was scarce. During 2013, cases had been reported in Bali, Indonesia, Java, the Pacific Ocean (Micronesia, New Caledonia), the Philippines and Singapore [6]. Several states in India (Gujarat, Kerala, Nad, Odisha and Tamil) also reported an increased number of cases [7]. This is of relevance because of the substantial passenger traffic between the Indian community of Saint Martin and India, and indicates a risk of importing cases from India.

The timeliness of the alert, despite the simultaneous dengue fever epidemic, was made possible by three factors. The first was the health event intelligence system organised in the French West Indies, which aims to confirm and assess the risk of every unusual health signal transmitted (via telephone or email) by a health professional or a patient [8].

The second was the awareness of the risk of introduction and transmission of CHIKV on all Caribbean islands, since the major epidemic on Reunion Island in 2006 [9]. Between 2006 and 2009, nine travellers entering the French West Indies were diagnosed with confirmed CHIKV infection, one of them on Saint Martin [10]. Seven of them had arrived from Reunion Island and two from India. Vector control activities were implemented around each of these imported cases, and none led to local transmission. Although Girod and Coll confirmed vector competence of *Ae. aegypti* (the only vector mosquito genus present in the French West Indies) for CHIKV transmission [11], no indigenous transmission of this virus had been observed in the Americas since [12].

The third factor of timeliness was the chikungunya preparedness plan which is similar to that for DENV, integrating activities of surveillance, laboratory, communication, patient care and vector control. Following the alert of 2006 and the risk of virus spread from potential other imported cases, the Cire and ARS teams of all the French territories in the Americas had decided to implement a preparedness and response plan for CHIKV introduction. Suspected and confirmed case definitions were standardised, laboratory resources for confirmation identified in the region, and first response activities implemented. This plan ('Programme de Surveillance, d'Alerte et de Gestion' (Psage)), based on the Integrated Management Strategy recommended by the World Health Organization for DENV, included four phases of increasing epidemic risk. At the time of the outbreak in 2013, Saint Martin was in the first risk phase, which required reporting of suspected and confirmed cases of CHIKV by clinicians and diagnostic laboratories to the local Health Event-dedicated cell of the corresponding Regional Agency for Health (Martinique, Guadeloupe or French Guiana). Epidemiological and entomological investigations were to be conducted simultaneously in the neighbourhood of the reported cases.

This regional alert has a wider impact: if the epidemic continues to spread in the Caribbean region and the Americas during the coming months, imported cases in southern Europe may have the potential to cause local outbreaks during the summer season.

Conflict of interest

None declared.

Authors' contributions

Sylvie Cassadou and Martine Ledrans: management and coordination of the investigations. Severine Boucau: implementation of investigations. Marion Petit-Sinturel: data management. Patricia Huc: blood sample taking and management. Isabelle Leparc-Goffart: Chikungunya tests (RT-PCR and Serology).

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Importance of case definition to monitor ongoing outbreak of chikungunya virus on a background of actively circulating dengue virus, St Martin, December 2013 to January 2014

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Since 5 December 2013, chikungunya virus (CHIKV) has been demonstrated to circulate in the Caribbean, particularly on Saint Martin. This region is facing a concomitant dengue virus (DENV) outbreak. Of 1,502 suspected chikungunya cases, 38% were confirmed chikungunya and 4% confirmed dengue cases, with three circulating serotypes. We report in addition 2.8% CHIKV and DENV co-infections. This study highlights the importance of the case definition for clinicians to efficiently discriminate between DENV infection and CHIKV infection.

On 5 December 2013, the first confirmed autochthonous cases of chikungunya virus (CHIKV) infection were reported in the Caribbean, on the island of Saint Martin, by the French National Reference Center for Arboviruses (IRBA, Marseille) [1]. Before that time, only imported cases of Chikungunya had been detected in the Americas.

CHIKV is a mosquito-transmitted virus (arbovirus) of the *Togaviridae* family and Alphavirus genus. It was first isolated from humans and mosquitoes in 1952/53 during an epidemic of febrile polyarthralgia in Tanzania [2]. CHIKV is endemic in some parts of Africa and causes recurrent epidemic waves in Asia and on the Indian subcontinent.

The Caribbean region, with tropical climate and the presence of *Aedes aegypti* mosquito vectors is endemic for dengue virus (DENV), another arbovirus. Since the re-emergence of dengue in the Caribbean subregion in the 1970s and the first dengue outbreak identified on Saint Martin in 1977, this arbovirus has been responsible for multiple waves of outbreaks on this island [3].

The latest epidemic of DENV on the island started in January 2013.

Both chikungunya and dengue disease have similar clinical symptoms, which makes the clinical diagnosis complex, although differences exist. In the context of an emerging virus in a region where another arbovirus is already endemic and actively circulating, the case definition (Table 1) is crucial to follow the dynamics of the new outbreak. This report shows the efficiency of the established case definition in the chikungunya outbreak on Saint Martin, and presents the incidence of co-infection of DENV and CHIKV.

Virological findings during the chikungunya and dengue outbreak

The French National Reference Centre for Arboviruses in Marseille received all samples from Saint Martin fitting the CHIKV case definition. However, both DENV and

TABLE 1

Case definition for clinical suspected chikungunya and dengue cases, Saint Martin, 2013

Chikungunya virus infection	Dengue virus infection
Fever higher than 38.5 °C of sudden onset	Fever higher than 38.5 °C of sudden onset
Articular pain in extremities	At least one of the following clinical signs: headache, arthralgia, myalgia, back pain, retro-orbital pain, musculo-articular pain
Absence of other aetiological causes	Absence of other aetiological causes

TABLE 2

Strategy for laboratory diagnosis of chikungunya and dengue virus infection, Saint Martin, 2013

Period between start date of clinical symptoms and sample date	Laboratory tests performed
<5 days	Real-time RT-PCR
Between 5 and 7 days	Real-time RT-PCR and serology
>7 days	Serology

CHIKV diagnosis was done on every sample because of the local epidemiological context and the clinical similarities between the two diseases. According to the date of clinical symptoms onset and the sampling date, viral genome and/or IgM and IgG detection techniques were performed following the strategy described in Table 2, by using, respectively, real-time RT-PCR described previously [4,5] and in-house ELISA (MAC ELISA for IgM and indirect IgG ELISA) [6]. The samples were mostly early samples, with 87% of samples taken less than seven days after the onset of symptoms.

The virological results are presented in Figure 1. A total of 1,502 suspected chikungunya cases samples were received between week 43 of 2013 (4 December 2013) and week 05 of 2014 (31 January 2014). Of those, 570 were confirmed chikungunya cases (38%), and 65 were confirmed dengue cases (4%). Confirmed cases were defined as patients with RT-PCR-positive or IgM- and IgG-positive samples. The median age of confirmed chikungunya cases was 39 (range: 10 days–73) and 60% were female. There were only three severe cases which required hospitalisation.

In Saint Martin, three serotypes of DENV co-circulated during this outbreak: DENV1, DENV2 and DENV4, with serotype 1 predominating. The proportion of the different DENV serotypes detected during this period is presented in Figure 2.

There were an additional 16 patients with confirmed co-infection of CHIKV and DENV (not included in Figure 1), i.e. with both viral genomes detected in the same blood sample. Those cases corresponded to the clinical case definition (Table 1) and were not severe cases. The co-infecting DENV was predominantly serotype 1, following the distribution observed in the mono-infected patients with 10 DENV1, two DENV2 and four DENV4 infections. Of these co-infected cases, four patients were two pairs of relatives living at the same address.

Discussion

The Caribbean region is currently facing an epidemic of CHIKV that started on Saint Martin and spread to Saint Barthelemy, Martinique, Guadeloupe and the Virgin Islands within a few weeks. This is the first time

that CHIKV circulation has been demonstrated in the Caribbean area and, more generally, the Americas. The genome of this circulating CHIKV strain was sequenced and belongs to the Asian genotype, suggesting Asia as the probable origin for the circulating virus [7].

The concomitant presence of DENV on this island leads to a difficult differential diagnosis for clinicians because both infections have similar clinical signs. Here, shortly after the start of the outbreak, an efficient case definition was set up that allowed monitoring of the emerging CHIKV outbreak on the background of actively circulating DENV.

A non-negligible proportion of co-infections were identified. Patients co-infected with CHIKV and DENV were previously reported in India, South-East Asia and Africa [8-10]. During the chikungunya epidemic in Gabon in 2007, a total of 3% of CHIKV-infected patients were also infected with DENV, both viruses being detected by RT-PCR. The CHIKV strain in Gabon belonged to the East Central South African genotype, contrary to the present Saint Martin virus, which belongs to the Asian

FIGURE 1

Confirmed chikungunya (n=570) and dengue (n=65) cases, Saint Martin, 4 December 2013–31 January 2014

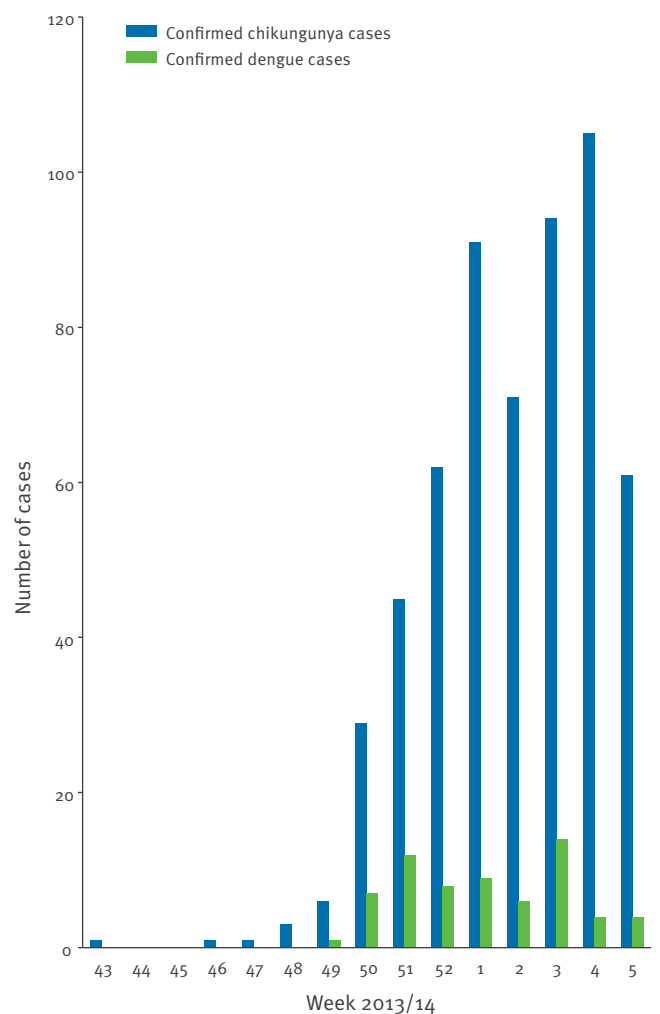
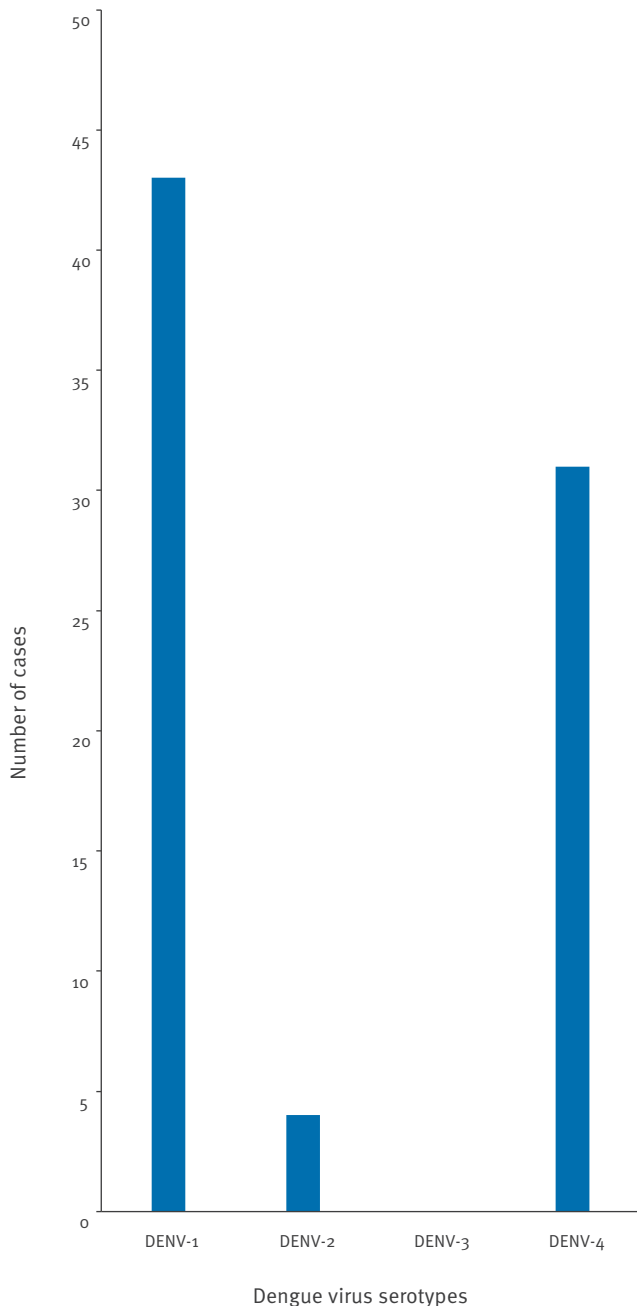


FIGURE 2

Distribution of circulating dengue virus serotypes, Saint Martin, 4 December 2013 to 31 January 2014 (n=78)



genotype. However, the number of co-infected cases in this current outbreak follows the same pattern, with 2.8% of CHIKV-infected patients also infected by DENV.

This study documents the importance of a clear case definition set up for clinicians to efficiently discriminate between DENV infection and CHIKV infection, thereby allowing good monitoring of the emerging outbreak by health authorities. With the presence of *Aedes* mosquitoes in most of the Americas, and intense circulation of the human population in this area, it is predicted that CHIKV will spread, and most probably in DENV-endemic areas.

Both emergences of dengue virus in France in 2010 and 2013 started with the arrival of a viraemic patient from the French Caribbean, which reflects the considerable exchange between Europe and the Caribbean [11,12]. The current chikungunya outbreak in the Caribbean likewise presents a threat of emergence of this disease in European countries, where the vector *Aedes albopictus* is already established.

Authors' contributions

RO, CMP, OF, SB, BT, OM, PH-A, SC and ILG participate to the study; RO, CMP, OF, ILG wrote the manuscript; PH-A and SC reviewed the manuscript.

Conflict of interest:

None declared.

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Cases of chikungunya virus infection in travellers returning to Spain from Haiti or Dominican Republic, April-June 2014

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Ten cases of chikungunya were diagnosed in Spanish travellers returning from Haiti (n=2), the Dominican Republic (n=7) or from both countries (n=1) between April and June 2014. These cases remind clinicians to consider chikungunya in European travellers presenting with febrile illness and arthralgia, who are returning from the Caribbean region and Central America, particularly from Haiti and the Dominican Republic. The presence of *Aedes albopictus* together with viraemic patients could potentially lead to autochthonous transmission of chikungunya virus in southern Europe.

We report 10 cases diagnosed with chikungunya virus (CHIKV) infection in Spain after returning from Haiti or the Dominican Republic. These are the first cases reported in Spain from travellers returning from Latin America and this should alert clinicians to consider CHIKV infection in any traveller with febrile illness or arthralgia returning from Central America and/or the Caribbean, particularly from Haiti and the Dominican Republic.

Case reports

Case definition

In this report, a probable case was defined as a person who was residing in or visited epidemic area within 15 days before onset of symptoms, was presenting with fever and arthralgia or arthritis, and had a positive IgM CHIKV antibody test result; a confirmed case was defined as a positive tests for one of the laboratory criteria, irrespective of clinical manifestations: (i) presence of viral RNA, (ii) specific IgM antibodies or (iii) four-fold increase in IgG titres in paired samples.

Clinical and epidemiological data

Between April and June 2014, 10 patients were diagnosed with chikungunya in Spain. Their age ranged from 21 to 57 years (mean age: 45.7) and six were male. All patients presented with fever ($>37.7^{\circ}\text{C}$) and arthralgia. Four patients also had an itchy rash. Clinical and epidemiological features of the cases of chikungunya are presented in the Table.

Travel history

Nine cases resided in Catalonia and one in Cuenca, Spain. However, all 10 had a history of recent travel to Haiti and/or the Dominican Republic and for all symptoms had started either when abroad or within five days of their return to Spain.

Seven of the 10 cases had travelled to the Dominican Republic, while two had been to Haiti. One case had visited both of these countries. The seven cases whose travel was limited to the Dominican Republic had done short trips there, which lasted less than a month. These cases included two persons who were visiting friends and relatives (VFR) in very small village near Santo Domingo and another person VFR who stayed in San Cristobal (south of the Dominican Republic). The remaining four of the seven cases had travelled separately all over the Dominican Republic, one during a short period for work and three as tourists. The two cases who had only visited Haiti had been there as part of their job, as they worked for the same company. During their stay, they lived together in the town of Jacmel for eight months before returning to Spain. The case who had been both to Haiti and the Dominican Republic was a tourist who had travelled there for a total period of four months.

TABLE

Clinical and epidemiological characteristics of cases of chikungunya in travellers returning from Haiti and/or the Dominican Republic, Spain, April–June 2014

Cases	Sex	Approximate age in years	Country visited	Duration of stay (days)	Clinical symptoms ^a	Diagnosis ^{b,c}	Treatment required
1	M	In the 40s	Haiti	240	Fever, rash, arthralgia	PCR	NSAID
2	M	In the 50s	Haiti	240	Fever, rash, arthralgia	Serology	NSAID
3	F	In the 30s	Dominican Rep.	15	Fever, rash, arthralgia	PCR	Nothing
4	F	In the 50s	Dominican Rep.	15	Fever, arthralgia	PCR	NSAID
5	M	In the 50s	Dominican Rep.	15	Fever, headache, arthralgia	Serology	Nothing
6	M	In the 40s	Dominican Rep./Haiti	120	Fever, rash, arthralgia	Serology	NSAID
7	M	In the 40s	Dominican Rep.	5	Fever, weakness, polyarthralgia	Serology	Steroids
8	F	In the 50s	Dominican Rep.	7	Fever, arthralgia	PCR	NSAID
9	M	In the 40s	Dominican Rep.	24	Fever, headache, polyarthralgia	PCR	NSAID
10	F	In the 20s	Dominican Rep.	30	Fever, arthralgias	Serology	Nothing

Dominican Rep.: Dominican Republic; F: female; M: male; NSAID: Non-steroidal anti-inflammatory drug; PCR: polymerase chain reaction. For all 10 cases, symptoms started either when abroad or within five days of their return to Spain.

^a Fever was defined as a temperature $\geq 37.7^{\circ}\text{C}$.

^b Diagnosis by PCR was done by a real-time reverse transcription-PCR (RT-PCR) (Realstar CHIKV kit, Altona diagnostics).

^c Diagnosis by serology included detection of both IgM and IgG against CHIKV in the first sample obtained, using a commercial immunofluorescence assay (Euroimmun). These cases were classified as probable cases.

Laboratory confirmation

For all cases, dengue virus infection was excluded through either polymerase chain reaction (PCR) or serological tests. In five of the 10 cases, chikungunya diagnosis was confirmed by real-time reverse transcription-PCR (RT-PCR) (Realstar CHIKV kit, Altona diagnostics). In the five remaining patients, chikungunya diagnosis was based both on IgM and IgG antibodies against CHIKV, which were detected by immunofluorescence (Euroimmun). PCR was not performed for such patients because the first diagnostic samples were obtained between 10 and 21 days after the onset of symptoms and the probability of viraemia was very low.

Treatment

Although their condition significantly improved one or two weeks after symptom onset, the majority of cases required anti-inflammatory therapy. Three weeks after the onset of symptoms, only three patients were still taking anti-inflammatory drugs and one of them required steroids therapy during 15 days due to the persistence of polyarthralgia.

Background

CHIKV is an arbovirus of the genus Alphavirus transmitted by *Aedes* mosquitoes (mainly *Ae. aegypti* and *Ae. albopictus*) [1].

Clinical manifestations of chikungunya

The disease caused by CHIKV has an incubation time that ranges from one to 12 days, with an average of two

to four days [2] and clinical presentation has similarities with dengue fever. Chikungunya is characterised by fever, headache, rash and both acute and persistent arthralgia. Polyarthralgia is common in cases CHIKV infection and is the most disabling symptom [2]. Around 75% of infections are symptomatic [3] and general complications are rare but include myocarditis, hepatitis, ocular disorders, central nervous system involvement (encephalitis), and haemorrhagic fever [4]. Although the mortality rate associated with CHIKV is low, the arthralgia can persist or can recur for weeks or months [5] and the likelihood of developing persistent arthralgia is highly dependent on age, being more prevalent in those older than 45 years-old [2].

Diagnosis

The diagnosis should be based on clinical, epidemiological and laboratory criteria [2]. The laboratory confirmation is crucial to distinguish from other disorders with similar clinical manifestations, such as dengue fever, other diseases caused by alphaviruses, or malaria. In the acute phase of illness, detection of viral nucleic acid in serum by RT-PCR is possible [6]. After this period, diagnosis relies on detection of specific antibodies against CHIKV [7-8]. Laboratory confirmation of CHIKV infection is usually achieved by detection of viral genome or demonstration of seroconversion in paired serum samples [9].

Geographical distribution of chikungunya virus

Until 2005, CHIKV infection was endemic in some parts of east Africa and southeast Asia and cases were also reported from the Indian subcontinent [2,10]. Following outbreaks of chikungunya in islands of the Indian Ocean and in peninsular India in 2005 [11], the virus also caused localised outbreaks in some countries in Europe, such as Italy (2007) and France (2010) [12-13]. Before 2013, CHIKV infections had not been detected in the Americas but in December of that year, the first confirmed autochthonous case of CHIKV was reported in the Caribbean, in Saint Martin [14]. Since then, almost 800 confirmed cases of CHIKV infection have been reported from Saint Martin [15] and the virus has spread to the whole Caribbean. As of the end of June 2014, almost 255,000 suspected cases have been reported from the Latin Caribbean and there are almost 180,000 suspected cases in the Dominican Republic

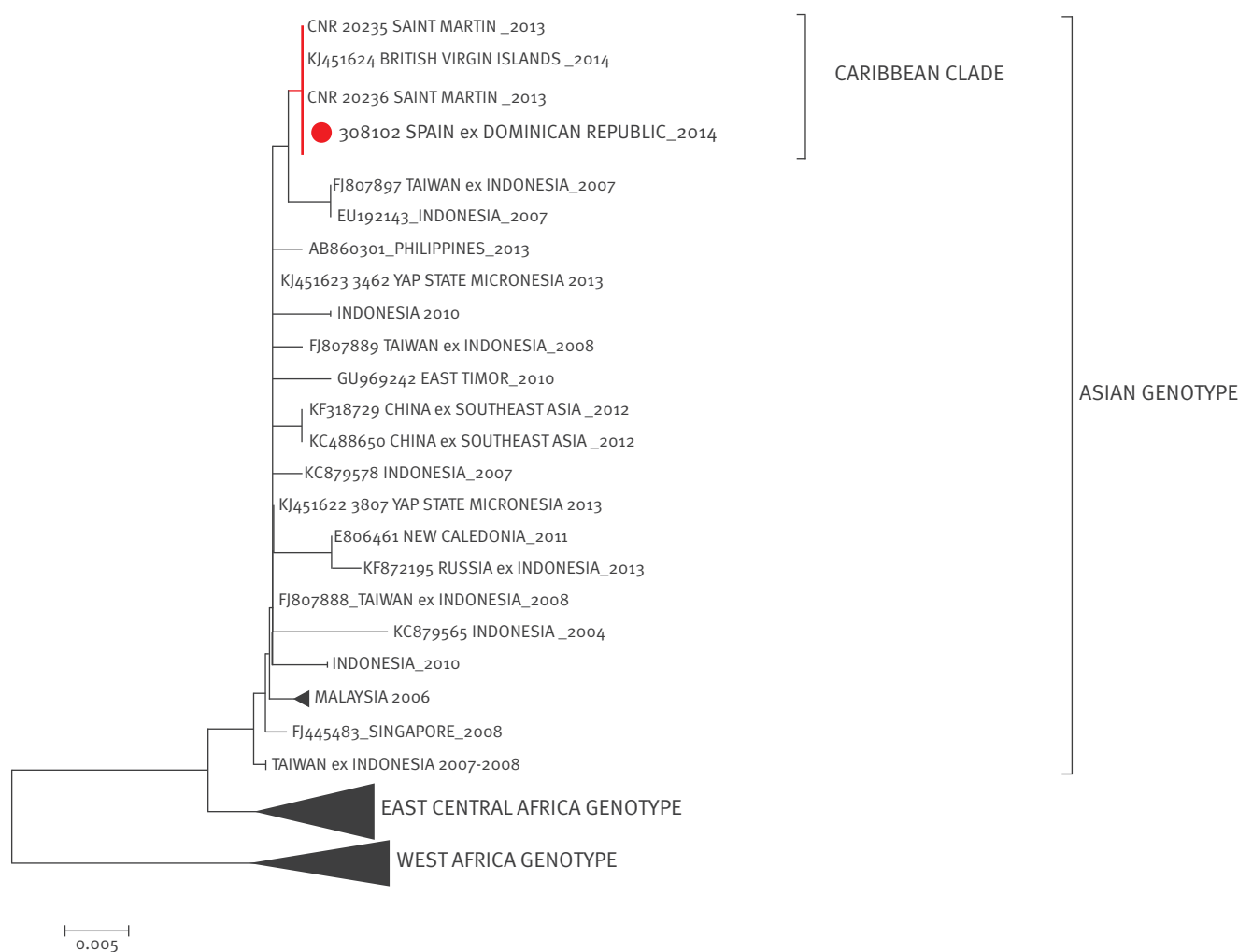
and Haiti, with 18 confirmed cases in the Dominican Republic and 14 in Haiti [15-16].

Investigation of the chikungunya virus sequence derived from a case

A PCR targeting the partial envelope protein (E) 1 gene was done in addition to the real-time RT-PCR for one case (case 9), who had travelled to the Dominican Republic [17]. Following amplification and sequencing of the gene, basic local alignment search tool (BLAST) analysis revealed a 100% similarity index of the case's sequence with sequences from strains recently identified in the British Virgin Islands (strain 99659; GenBank accession number: KJ451624) and Saint Martin (strain CNR-20235/STMARTIN/2013, retrieved from the European virus archive (<http://www.european-virus-archive.com>)) [18]. Phylogenetic analysis, using MEGA5 software showed the strain affecting the patient to be of the Asian genotype, and in the

FIGURE

Phylogenetic analysis of a sequence derived from a case of chikungunya virus infection in a traveller returning from the Dominican Republic to Spain, April 2014



The phylogenetic tree was constructed by neighbour-joining method and based on partial (450 nt) sequences of the chikungunya virus Envelope protein 1 gene. The sequences analysed included one derived from the case reported here, which is highlighted (sequence 308102/2014), and 90 sequences retrieved from Genbank. Sequences from East and Central and West Africa were collapsed.

phylogenetic tree, the sequence derived from the case clustered together with other CHIKV sequences from the Caribbean (Figure). The sequence was deposited in GenBank under accession number KM192348.

Discussion

We report 10 cases of chikungunya in Spain between April and June 2014. Five of these can be considered as laboratory confirmed based on a positive specific real-time RT-PCR. The other five that tested positive for both IgM and IgG CHIKV antibodies can be classified as probable cases.

All cases had a clear epidemiological link to the Dominican Republic and/or Haiti, two countries where they had recently travelled and which were concurrently affected by chikungunya. Symptom onset for all cases occurred either before returning to Spain or within a period compatible with infection abroad, based on the incubation time. Phylogenetic analysis of a viral sequence derived from one of the cases moreover showed 100% similarity with sequences from strains recently identified in the Caribbean.

After December 2013, when autochthonous transmission of CHIKV was first reported in Saint Martin, the virus spread within a few weeks to most countries of the Caribbean, where an outbreak is currently taking place [18]. A concomitant dengue outbreak in the region complicates differential diagnosis. Chikungunya presents a good example of the interaction between globalisation and emerging infections. During the last 10 years, the virus has spread throughout the Indian Ocean, Asia, and localised outbreaks have also been reported in Europe [2]. Local transmission has been detected in the Americas in recent months. It is predicted that CHIKV will spread in most American areas where *Aedes* mosquitoes are endemic [14].

Cases of autochthonous transmission have not been reported in Spain but imported cases from countries affected by CHIKV have been documented in the past years [19,20] and a retrospective study reported 14 to 15 cases per year in the period between 2006 and 2007 [21]. Since April 2014 however, due to the situation in the Caribbean region, the numbers of cases have increased and in addition to the cases presented here further more recent cases have occurred (data not shown). According to last data from the World Tourism Organization (data from 2008–2012), Spain is one of the European countries with a largest number of travellers to Haiti and the Dominican Republic [22]. Moreover, the presence of immigrants in Europe from the Caribbean [23, 24] may also account for trips to these countries. The number of imported cases of CHIKV into Europe is likely to increase in the following weeks.

Aedes aegypti, one of the main vectors of CHIKV, is present in some areas of Europe, such as Madeira [25]. *Ae. albopictus*, the other vector, is already established in various countries in Europe, such as Italy, the south of

France and some regions in Spain [26, 27–29]. In Spain, the mosquito is found in most parts of Catalonia, the region where most of our cases (9/10) were residing, and in the Balears islands as well as some territories of Murcia and Valencia [26]. Although *Ae. Albopictus* is currently not established in Cuenca, where one of the cases lived, this town is approximately 200 km away from Valencia.

The presence of a chikungunya vector together with travellers, who are still in the period of viraemia, as for five of our cases, could be a source of local transmission of CHIKV infection. In fact, an outbreak of autochthonous CHIKV infection already occurred in north-eastern Italy in 2007 after an index case arrived from India [30]. This led to an estimate of 254 locally-acquired infections [30]. With vectors established in parts of Europe and the intense circulation of people between this continent and America, there is a threat for new localised outbreaks of CHIKV infection in Europe [18].

At this time, surveillance in the Catalonian region [31] where the vector is established is based on active-case finding. The surveillance is activated when either a confirmed case is detected or when a probable case in Catalonia could be viraemic. Moreover, primary healthcare centres belonging to the local area where the probable or confirmed case is detected are warned and, in parallel, the regional government in Catalonia is trying to activate measures to control the vector in the affected areas.

The set up of a surveillance system that can accurately identify chikungunya cases presents difficulties since the symptoms of the infection are not very specific. However, although confusion between dengue and chikungunya is possible, in most cases the symptoms of chikungunya are specific enough to be recognisable in travellers by clinicians who are aware of the disease.

Conclusions

CHIKV infection might be suspected in any people returning from the Caribbean with fever, particularly if disabling arthralgias are present. In regions infested with *Ae. albopictus* or *Ae. aegypti*, health authorities should be aware of the risk of local outbreaks and the need to implement control measures for both vectors.

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Conflict of interest

None declared.

Authors' contributions

AR, CG, EA, AC, JAV, AM, MR, IP and JA took clinical care of the patients, since admission to hospital and at outpatient clinic once discharged. MJM, LF and MPSS, performed the laboratory investigations and phylogenetic analysis of the virus, JG and JAPM were the senior supervisor of the article. All authors participated in writing the manuscript.

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Large number of imported chikungunya cases in mainland France, 2014: a challenge for surveillance and response

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During the summer of 2014, all the pre-requisites for autochthonous transmission of chikungunya virus are present in southern France: a competent vector, *Aedes albopictus*, and a large number of travellers returning from the French Caribbean islands where an outbreak is occurring. We describe the system implemented for the surveillance of chikungunya and dengue in mainland France. From 2 May to 4 July 2014, there were 126 laboratory-confirmed imported chikungunya cases in mainland France.

In November 2013, locally acquired cases of chikungunya were laboratory-confirmed in the French Caribbean island of Saint Martin [1]. The chikungunya virus rapidly spread in the surrounding French territories (Martinique, Guadeloupe, Saint Barthélemy and French Guiana) in December 2013 and then in most of the islands of the Caribbean [2,3]. By 15 June 2014, there were more than 80,000 clinically compatible cases in the French Caribbean Islands, based on the estimation of the sentinel surveillance [4]. Given the epidemic situation in the French Caribbean, and due to the large amount of travel between mainland France and the Caribbean, it is expected that a large number of chikungunya cases will be imported to mainland France in 2014.

During the summer of 2014, all the pre-requisites for autochthonous transmission of chikungunya virus, and to a lesser extent, dengue virus, will then be present in southern France: a competent vector [5], a large number of viraemic travellers, and favourable climatic conditions for mosquito reproduction and viral replication in the mosquitoes. The likelihood of chikungunya transmission in mainland France is therefore particularly high.

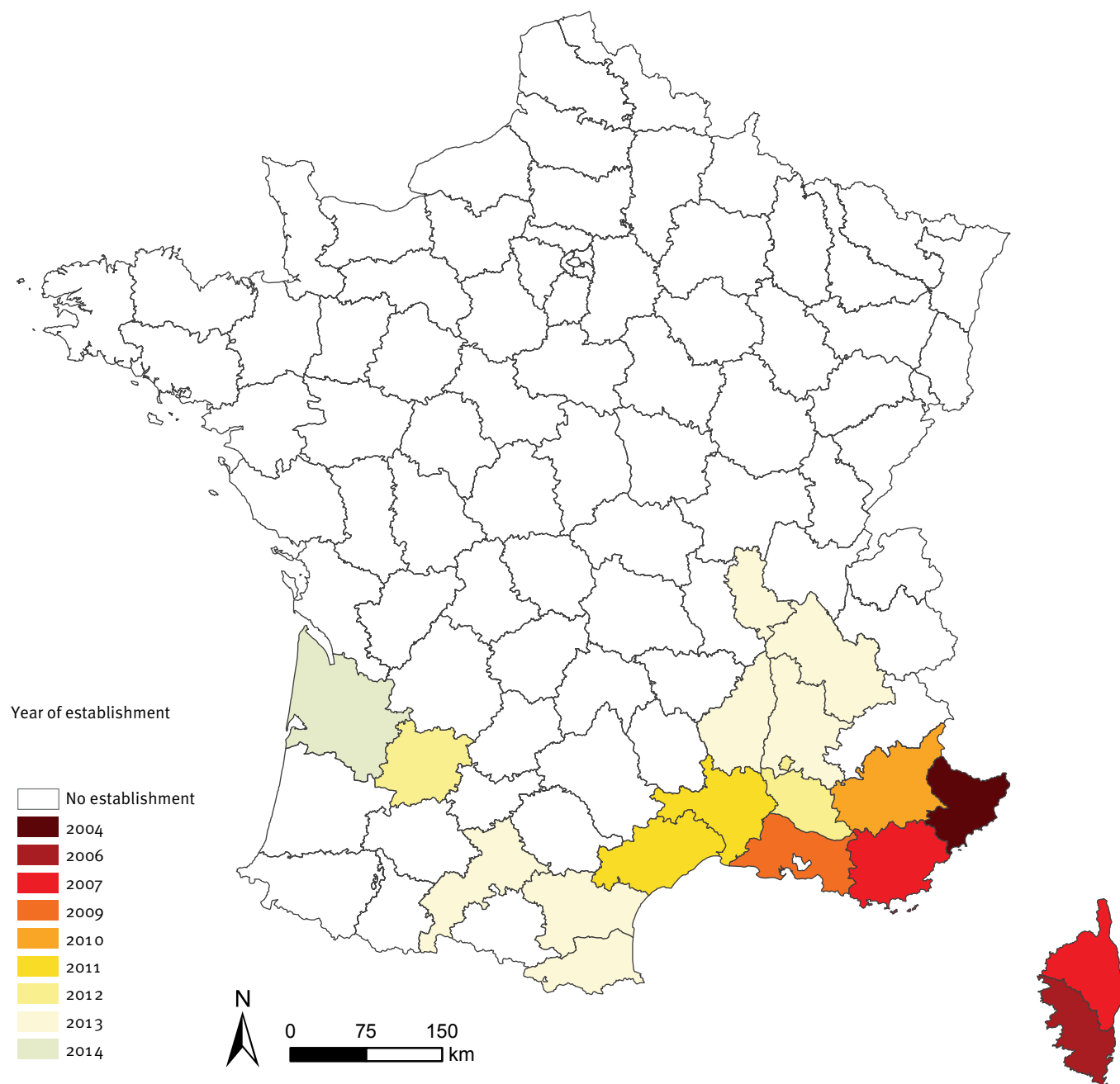
Surveillance of chikungunya and dengue in mainland France

Chikungunya and dengue are mosquito-borne viral diseases, transmitted by *Aedes* mosquitoes, in particular *Aedes aegypti* and *Aedes albopictus*, the latter being present in Europe [6,7]. Since it was identified in 2004 in the French administrative district of Alpes-Maritimes, *Ae. albopictus* has continued to spread in southern France [8,9].

Since 2006, in response to *Ae. albopictus* establishment in southern France, the French Ministry of Health has implemented a dengue and chikungunya preparedness and response plan to monitor and prevent the risk of dissemination of the two viruses in mainland France [10]. Because the two diseases present a number of similarities regarding the clinical and entomological

FIGURE 1

Establishment of *Aedes albopictus*, by administrative district and year, mainland France, 2004–2014



Source: IGN-GéoFLA, 1999; French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS), 2014.

features, a common system has been set up comprising entomological and epidemiological surveillance.

Entomological surveillance for chikungunya and dengue

The entomological surveillance is operated by public local structures of mosquito control, under the coordination and responsibility of the Ministry of Health.

The presence and the spread of *Ae. albopictus* is monitored using ovitraps placed along the French Mediterranean coastline and land inwards along

motorways. Traps are checked at least monthly for presence of *Ae. albopictus* eggs. Mosquitoes and eggs are not tested routinely for the presence of dengue and chikungunya viruses.

The administrative districts, according to the year of establishment of *Ae. albopictus*, are shown in Figure 1: from one district in 2004, *Ae. albopictus* has become established in 18 administrative districts in six regions (Provence-Alpes-Côte d'Azur, Corsica, Languedoc-Roussillon, Rhône-Alpes, Aquitaine, Midi-Pyrénées) in 2014.

Epidemiological surveillance for chikungunya and dengue

A suspected case is defined as a person with acute fever (>38.5 °C) and joint pains (chikungunya) or at least one of the following symptoms: headache, retro-orbital pain, joint pains, myalgia or lower back-pain (dengue), not explained by another medical condition. For both diseases, cases are confirmed by serology (IgM positive or a fourfold increase in IgG titre) or detection of viral nucleic acids in plasma by real-time reverse transcription polymerase chain reaction (RT-PCR), or for dengue, a positive dengue nonstructural protein 1 (NS1) antigenic test.

The surveillance system aims to prevent or to contain autochthonous transmission of dengue and chikungunya, and comprises three components:

- nationwide year-long mandatory notification of laboratory-confirmed cases of chikungunya and dengue;
- seasonal enhanced surveillance in the administrative districts where the vector is established.

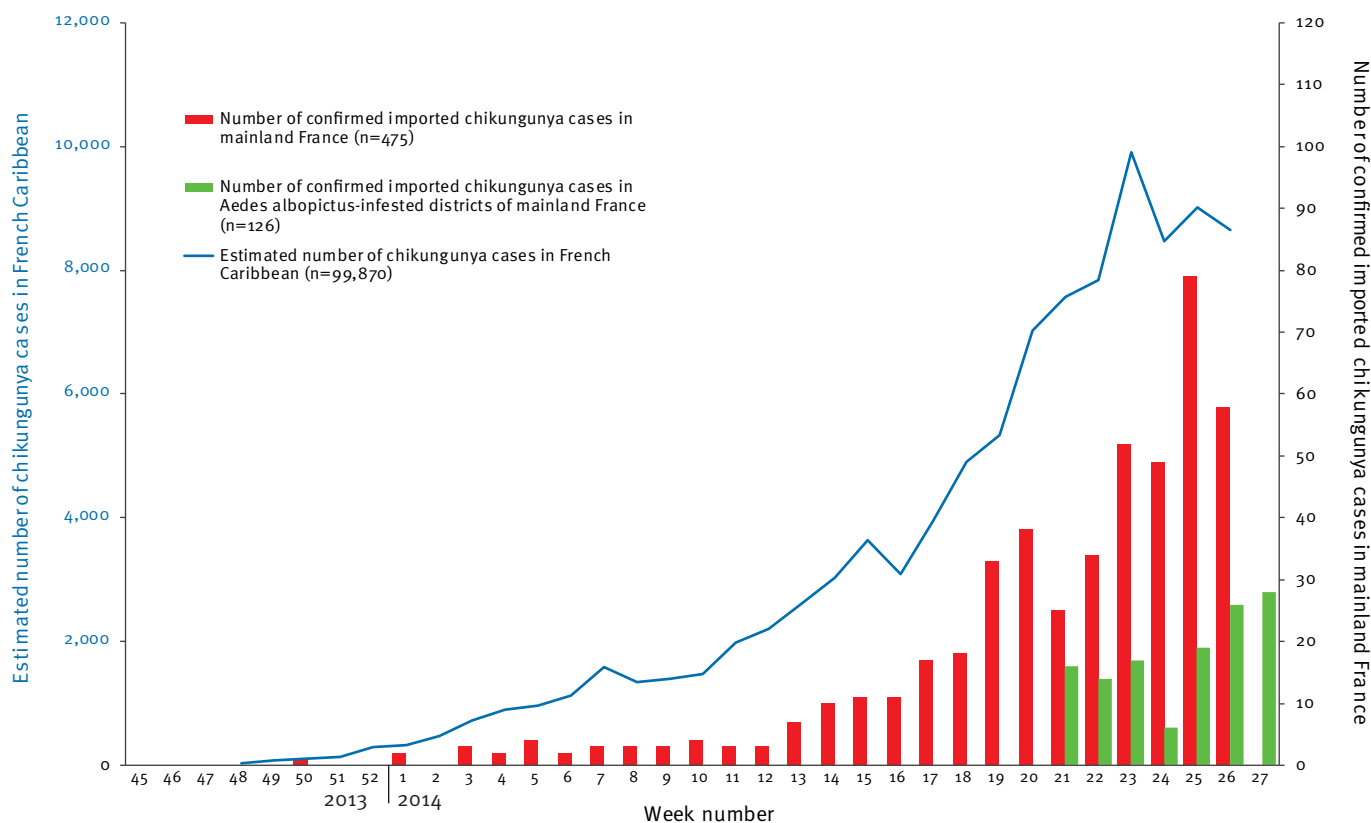
From May to November, when the vector is active, all suspected imported cases must be immediately reported to the regional health authorities (Agences Régionales de Santé, ARS). Appropriate vector control measures are then implemented within 200 metres of the places visited by the patients during the likely viraemic period (from the day before until seven days after the onset of symptoms [11]), without waiting for laboratory confirmation of the infection;

- daily reporting from a network of laboratories of the results of chikungunya and dengue serological or RT-PCR tests to the French Institute of Public Health Surveillance (Institut de veille sanitaire, InVS). This catches cases who have not been reported through the notification system and the seasonal enhanced surveillance, and thus serves to improve the completeness of reporting of the surveillance system.

The notification of a laboratory-confirmed locally acquired case triggers immediate epidemiological and entomological investigations, in order to assess the

FIGURE 2

Laboratory-confirmed imported chikungunya cases in mainland France^a, laboratory-confirmed imported chikungunya cases in *Aedes albopictus*-established districts in mainland France during the period of vector activity^b and estimated number of clinically compatible chikungunya cases in the French Caribbean^c



^a Per week, week 45 2013 to week 26 2014 (1 November 2013 to 27 June 2014), source: laboratory network. Data for week 26 2014 are not yet consolidated and are not available for week 27 2014.

^b Per week, weeks 18 to 27 2014 (2 May to 4 July 4 2014), source: enhanced surveillance.

^c Per week, week 48 2013 to week 26 2014 (25 November 2013 to 29 June 2014). Data are not available for week 27 2014, source: French Caribbean sentinel surveillance.

TABLE 1

Suspected and laboratory-confirmed cases of chikungunya and dengue, by region involved in seasonal enhanced surveillance, mainland France, 2 May–4 July (weeks 18 to 27) 2014

Regions	Number of administrative districts where <i>Aedes albopictus</i> is established	Resident population in administrative districts where the vector is established ^a	Number of suspected cases	Number of laboratory-confirmed imported cases		Number of laboratory-confirmed autochthonous cases	
				Chikungunya	Dengue	Chikungunya	Dengue
Provence-Alpes-Côte d'Azur	5	4,777,464	121	43	17	0	0
Corsica	2	314,486	4	0	0	0	0
Languedoc-Roussillon	4	2,592,890	55	28	6	0	0
Rhône-Alpes	4	3,764,718	76	27	12	0	0
Aquitaine	2	1,794,528	31	14	5	0	0
Midi-Pyrénées	1	1,260,226	63	14	7	0	0
Total	18	14,504,312	350	126	47	0	0

^a Source: French national institute of economic and statistical information (Institut national de la statistique et des études économiques, INSEE)

autochthonous transmission and to guide vector control measures. The investigation and control measures include: (i) active case finding in the neighbourhood of the case's residence and in other areas visited by the case; (ii) recommending personal protection measures for the viraemic patient; (iii) encouraging health professionals to screen suspected cases; (iv) carrying out perifocal vector control activities, within 200 metres of the case's residence, including destruction of mosquito breeding sites and spraying targeted at adult mosquitoes; (v) giving information to the public about personal protection and reduction of mosquito breeding sites.

Chikungunya cases in mainland France

Throughout mainland France, 475 laboratory-confirmed imported cases of chikungunya were notified through the laboratory network from 1 November 2013 (the month of confirmation of the first cases in Saint Martin) to 27 June 2014 (Figure 2), whereas during the whole of 2011 and 2012, there were 33 and 17 cases, respectively.

From 2 May to 4 July 2014, of 350 suspected cases who were notified to the regional health authorities, 126 were laboratory-confirmed imported cases of chikungunya and 47 laboratory-confirmed imported cases of dengue were detected in the *Ae. albopictus*-established districts (Table 1 and Figure 2). A large majority of the laboratory-confirmed imported cases of chikungunya arrived from the French Caribbean (85% (107/126), as shown in Table 2). More than 80% of cases (n=103) were in an *Ae. albopictus*-established district while potentially viraemic (the remaining 20% were diagnosed retrospectively). No autochthonous case has been confirmed to date. More information and updated surveillance results are provided on the InVS website [4].

Discussion

From 2006 to 2013, the number of laboratory-confirmed imported cases of chikungunya reported in *Ae. albopictus*-established districts from May to November ranged from 2 to 6 [4]. From 2 May to 4 July 2014, the number of laboratory-confirmed imported cases of chikungunya was much higher (126) than in previous years, as a consequence of the chikungunya outbreak in the Caribbean region.

Although no autochthonous case has been confirmed to date in 2014, the conditions required for autochthonous transmission of the chikungunya virus are met: the population in mainland France is immunologically naive to the virus; a competent vector exists, *Ae. albopictus* [5] and its distribution has been constantly and rapidly spreading for the past 10 years [10]; and the probability of introduction of the virus by travellers coming from affected areas is high. The possibility of occurrence of autochthonous transmission of arboviruses has been demonstrated in the recent past in southern France, with the identification of two autochthonous dengue cases in 2010 and one in 2013, as well as two autochthonous chikungunya cases in 2010 [12-14].

Passenger traffic between mainland France and Martinique and Guadeloupe is high, with more than 2.5 million plane passengers in 2013 [15]. During this summer of 2014 – when the mosquito is active – large numbers of travellers will return from the French Caribbean islands where an outbreak is currently occurring. Among them, a high proportion will possibly be viraemic upon their arrival, increasing the probability of the occurrence of autochthonous cases of chikungunya in the administrative districts where *Ae. albopictus* is established, and increasing the risk of a chikungunya outbreak in mainland France.

TABLE 2

Laboratory-confirmed chikungunya cases imported to mainland France, by place of origin, as of 4 July (week 27) 2014

Place of origin	Number of cases imported to mainland France
Guadeloupe	70
Martinique	36
Haiti	10
Dominican Republic	3
Tonga	1
Sierra Leone	1
Saint Martin	1
Indonesia	1
Côte d'Ivoire	1
Costa Rica	1
Cambodia	1
Total	126

Source: seasonal enhanced surveillance system, mainland France.

The preparedness and response plan developed in mainland France since 2006 has proved to be effective for the early detection of cases and implementation of vector control measures to prevent or contain autochthonous transmission of dengue and chikungunya viruses. However, it is currently challenged by the increased number of imported chikungunya cases. It is thus crucial to maintain a high level of mobilisation of all actors within the surveillance system. They are also an important source of information for the general population, to encourage the use of personal protection against mosquito bites and control of mosquito breeding sites.

The challenge that we face is to avoid the establishment of a local cycle of transmission in mainland France and, beyond, in other European areas where competent vectors are also present.

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Conflict of interest

None declared.

Authors' contributions

Marie-Claire Paty coordinates the chikungunya and dengue surveillance system at the national level. Brigitte Helyncx and Marie-Claire Paty co-drafted the manuscript. Colette Six, Francis Charlet, Guillaume Heuzé, Amandine Cochet, Axel Wiegandt, Jean Loup Chappert, Dominique Dejour-Salamanca, Anne Guinard, Pauline Soler, Véronique Servas, Martine Vivier-Darrigol, Martine Ledrans are responsible at regional level for the surveillance and epidemiological

investigations. Monique Debruyne, Oriane Schaal and Isabelle Leparc-Goffart are in charge of virological analysis and transmit the results on a daily basis to the surveillance teams. Charles Jeannin is an entomologist in charge of entomological investigations and mosquito control activities. Bruno Coignard reviewed the final document for accuracy. All authors contributed to the review of the manuscript and approved the final version.

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Chikungunya outbreak in the Caribbean region, December 2013 to March 2014, and the significance for Europe

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On 6 December 2013, two laboratory-confirmed cases of chikungunya without a travel history were reported on the French part of the Caribbean island of Saint Martin, indicating the start of the first documented outbreak of chikungunya in the Americas. Since this report, the virus spread to several Caribbean islands and French Guiana, and between 6 December 2013 and 27 March 2014 more than 17,000 suspected and confirmed cases have been reported. Further spread and establishment of the disease in the Americas is likely, given the high number of people travelling between the affected and non-affected areas and the widespread occurrence of efficient vectors. Also, the likelihood of the introduction of the virus into Europe from the Americas and subsequent transmission should be considered especially in the context of the next mosquito season in Europe. Clinicians should be aware that, besides dengue, chikungunya should be carefully considered among travellers currently returning from the Caribbean region.

Introduction

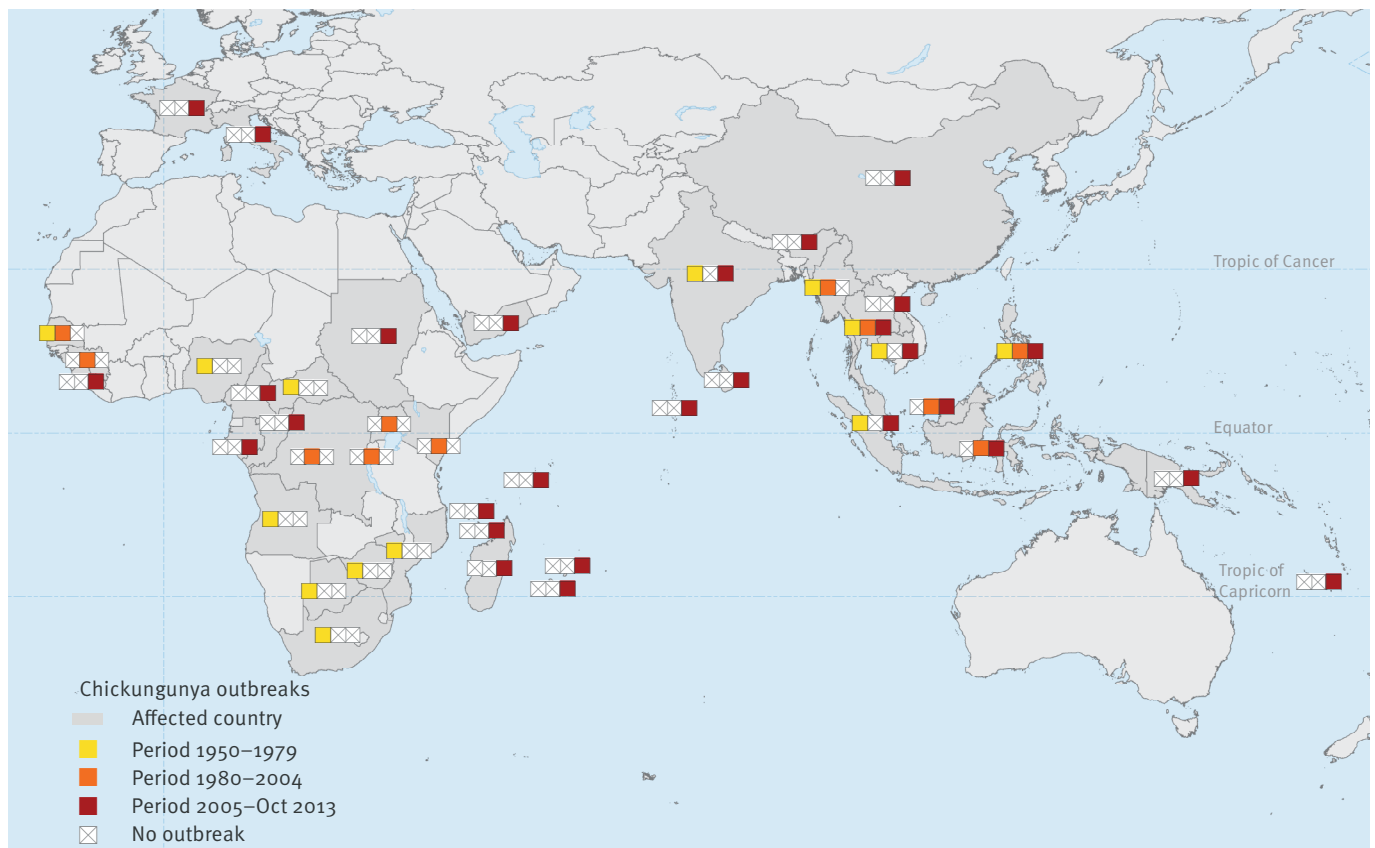
Chikungunya is a mosquito-borne viral disease caused by an alphavirus from the *Togaviridae* family. The virus is transmitted by the bite of *Aedes* mosquitoes, primarily *Aedes aegypti* and *Aedes albopictus*. The

typical clinical signs of the disease are fever and severe arthralgia, which may persist for weeks, months or years after the acute phase of the infection [1]. General complications include myocarditis, hepatitis, ocular and neurological disorders [2]. The detection and diagnosis of the disease can be challenging especially in settings where dengue is endemic. It was estimated that three to 25% of infected individuals are asymptomatic. Blood-borne transmission is possible [3,4] and mother-to-child transmission has also been reported in newborns of viraemic women who developed the disease within the week prior to delivery [5,6].

Chikungunya has been, up to 2005, found to be endemic in parts of Africa, south-east Asia and on the Indian subcontinent (see historical overview: Figure 1). Prior to 2005, outbreaks occurred mainly in the well-known endemic areas. From 2005 to 2006, large chikungunya outbreaks were reported from Comoros, Mauritius, Mayotte, Réunion and various Indian states (Figure 1). In 2013, chikungunya outbreaks occurred in a variety of geographic locations within India (Gujarat, Tamil Nadu, Kerala, Odisha states), Indonesia (East Jakarta, East Java), Micronesia (Yap), the Philippines archipelago, including the city of Manila, as well as Singapore, and the first evidence of autochthonous transmission

FIGURE 1

Historical overview of the chikungunya outbreaks prior to the emergence of the chikungunya virus in the Caribbean in December 2013



The Figure is based on references [29–81]. The detection of the chikungunya virus in the Caribbean in December 2013 constitutes the first finding of the virus in the Americas, therefore this region of the world is not shown on the map. Each square represents a particular period: the left square represents period 1950–1979, the middle square period 1980–2004 and the right square period 2005–October 2013. The squares are coloured yellow, orange and red respectively when an outbreak was reported in the literature. Otherwise the square is white-crossed.

in New Caledonia and Papua New Guinea was reported in June 2012 (Figure 1 and [7]). Autochthonous transmission in continental Europe was first reported from Emilia-Romagna, Italy, in August 2007 with more than 200 confirmed cases [8] and subsequently in 2010 in the Var, France with two confirmed cases [9]. In both areas the vector *Ae. albopictus* is established [10].

Three different genotypes of chikungunya virus, namely Asian, West African, and East/Central/South African (ECSA), have been identified. The acquisition of an A226V mutation in the envelope protein E1 of ECSA chikungunya virus, as observed in Réunion in 2005, increased the transmissibility of the virus by the widely distributed *Ae. albopictus* mosquitoes [11]. This mutated virus spread from the Indian Ocean to East Africa and Asia and was involved in the chikungunya outbreak in Italy [8]. Phylogenetic analysis proved that the chikungunya virus responsible for autochthonous cases in France belonged to the ECSA strain, but without the mutation at position 226 [9].

On 6 December 2013, two laboratory-confirmed cases of chikungunya without a travel history were reported on the French part of the Caribbean island of Saint Martin in the context of a dengue outbreak occurring on this island [12] and the virus spread since then to other islands in the Caribbean. This is the first documented outbreak of chikungunya with autochthonous transmission in the Americas. This paper aims to review the current epidemiological situation of chikungunya in the Caribbean region, to assess its significance for both the region and the European Union (EU) and to provide an historical overview of the geographical emergence of chikungunya.

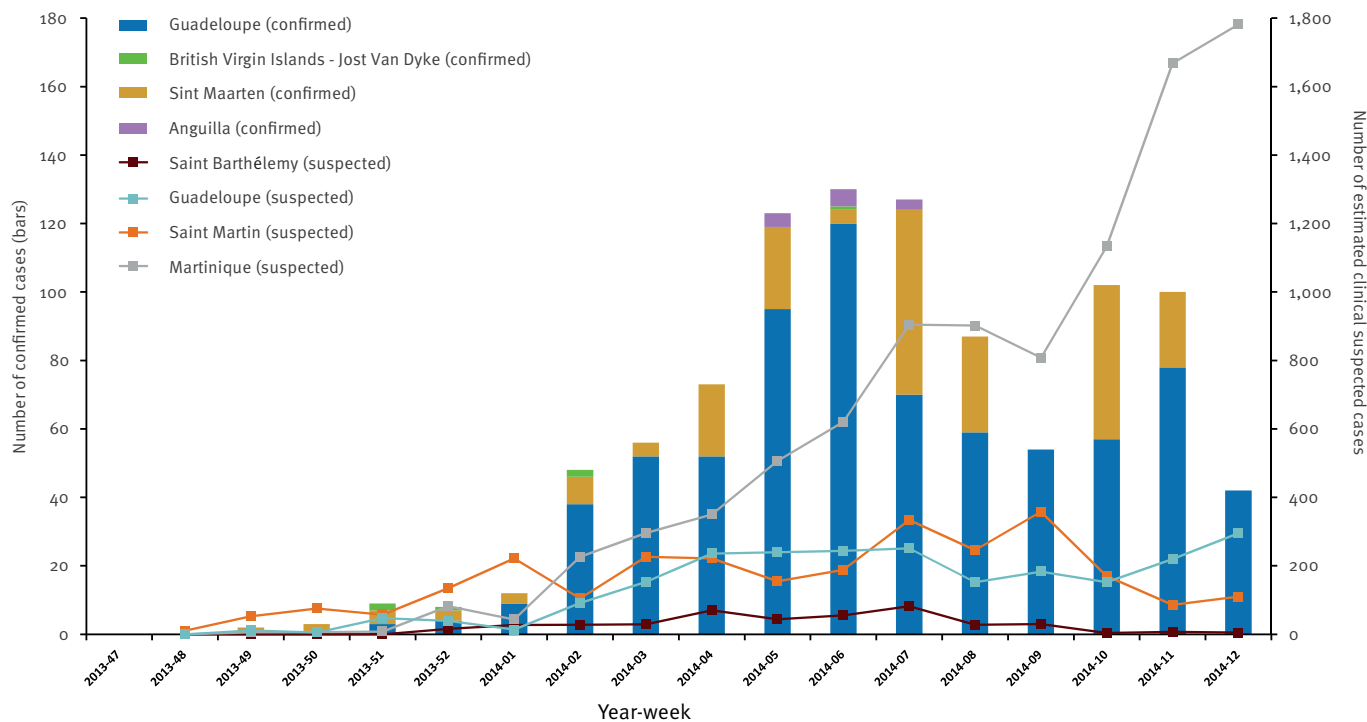
Epidemiology of chikungunya in the Caribbean

The Caribbean French overseas territories: French Guiana, Guadeloupe, Martinique, Saint Barthélemy and Saint Martin

The Caribbean French overseas territories include the islands Guadeloupe, Martinique, Saint Barthélemy

FIGURE 2

Number of confirmed and estimated suspected chikungunya cases reported in the Caribbean by week of sampling, 1 December 2013–23 March 2014



The period 1 December 2013–23 March 2014 corresponds to week 48 2013–week 12 2014. From week 5 2014 onwards the expert committee for emerging and infectious diseases of Martinique, Saint Barthélemy and Saint Martin recommended to focus the laboratory diagnostics on patients for which laboratory confirmation is needed to support case management. From then, the systematic confirmation of cases was ceased on these islands. Therefore the confirmed cases (bars) are only shown for Anguilla, Guadeloupe, Jost Van Dyke and Sint Maarten. Estimated numbers of suspected clinical cases (lines) are respectively provided for Guadeloupe, Martinique, Saint Barthélemy, and Saint Martin.

and Saint Martin, and French Guiana on the South American continent. Dengue surveillance and control are well established on the Caribbean French overseas territories.

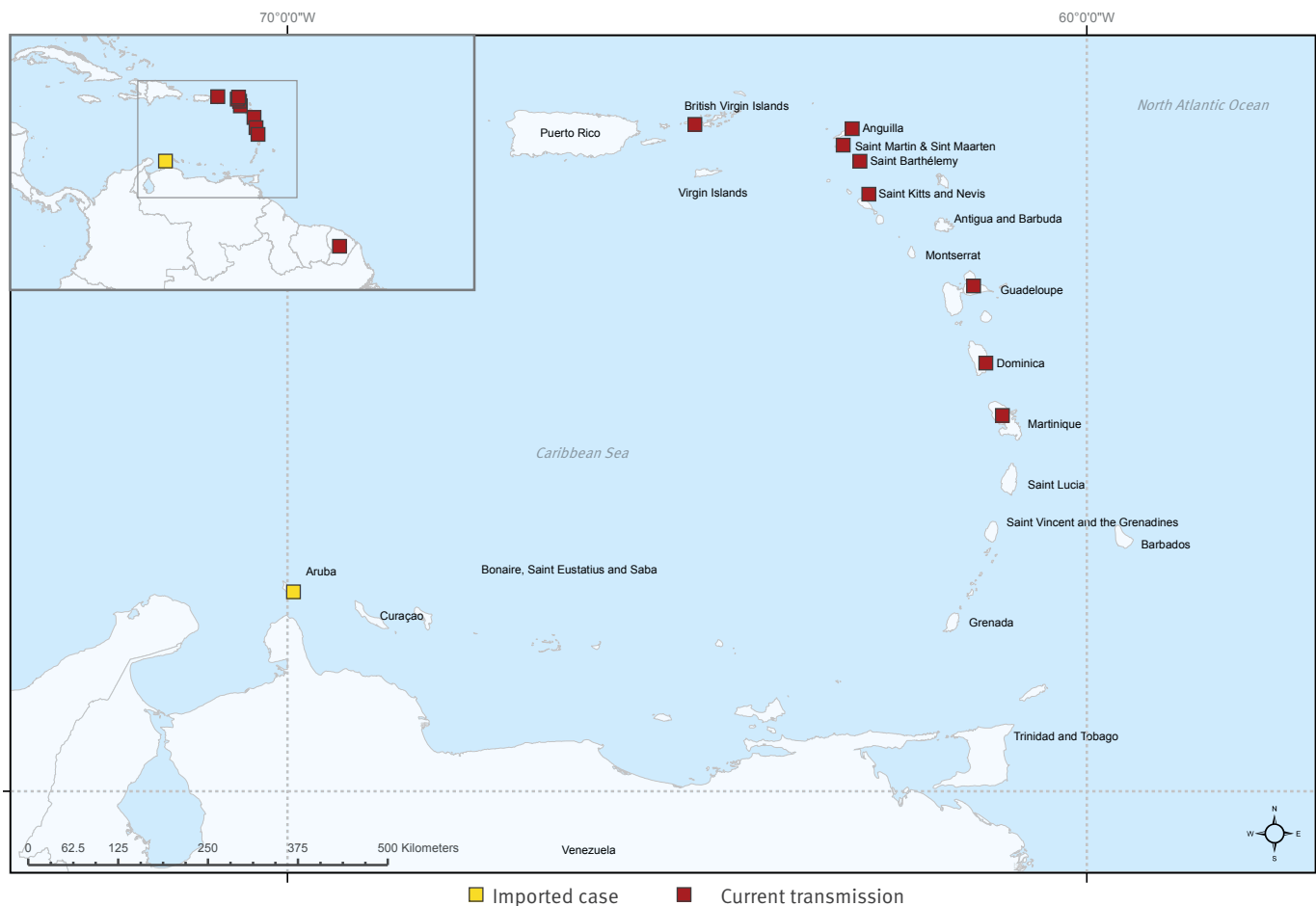
In mid-November 2013, the suspicion of autochthonous transmission of chikungunya virus on the island of Saint Martin was brought to the attention of the local health authorities. On 6 December 2013, a first suspected case of chikungunya occurring in the French part of the island was laboratory confirmed and an outbreak phase was declared the same day for Saint Martin.

Following this confirmation, enhanced surveillance for chikungunya cases was implemented not only in Saint Martin but also in the other Caribbean French overseas territories, because intense travel of people occurs between the affected island and these neighbouring territories. Based on the phase of the outbreak in the different territories – each territory declares the outbreak-phase based on their assessment/context – the following components of the surveillance system were either implemented or strengthened to achieve the early detection of suspected chikungunya cases

and to monitor the evolution of the epidemic. (i) During the pre-outbreak phase, i.e. when the first autochthonous cases are detected and laboratory confirmed, the surveillance focussed on systematic confirmation of cases. Therefore, general practitioners and medical microbiologists were invited to report all clinical suspected cases of chikungunya using a specific notification form. A clinical suspected case was defined as any individual with sudden onset of fever ($>38.5^{\circ}\text{C}$) with arthralgia and without any other aetiology. Laboratory investigations were systematically conducted on all clinical suspected cases. A confirmed case was defined as a clinical suspected case with laboratory confirmation, either a positive reverse transcription-polymerase chain reaction (RT-PCR) or a positive detection of IgM and IgG or both; (ii) once the outbreak was declared by the local authorities, i.e. the outbreak phase, the surveillance was performed through the weekly notification of clinical suspected cases by the sentinel network of general practitioners; in Saint Martin, all general practitioners and one paediatrician were asked to report the number of clinical suspected cases. Further all hospitals in the territories had to weekly notify emergency room visits for suspected cases, and hospital admissions for confirmed cases. The systematic

FIGURE 3

Local chikungunya transmission and imported cases in the islands of the Caribbean region and in French Guiana, 1 December 2013–23 February 2014



The period 1 December 2013–23 February 2014 corresponds to week 48 2013–week 8 2014.

laboratory confirmation of all suspected cases was ceased in week 5 2014 in Martinique, Saint Barthélemy and Saint Martin to prevent overloading the laboratories performing the diagnosis.

Strengthened surveillance enabled the detection of confirmed cases of chikungunya on French territories other than Saint Martin. Data were collected at the local level and regional level (i.e. the Regional Office of the French Institute for Public Health Surveillance, Fort-de-France, Martinique) in order to follow the progression of the virus in the different territories (French Guiana, Guadeloupe, Martinique, Saint Barthélemy, Saint Martin), to coordinate the activities and to harmonise common tools (questionnaires, templates, protocols) used during the pre-outbreak and outbreak management phases.

Epidemiological situation

Since the introduction of the chikungunya virus in Saint Martin and subsequent implementation of

enhanced surveillance, the first cases in Martinique, Guadeloupe, Saint Barthélemy and French Guiana were confirmed on 18, 24, 30 December 2013 and 19 February 2014 respectively. Since the start of the outbreak the number of suspected and confirmed cases increased indicating continuous transmission of the virus in all affected territories (Figure 2).

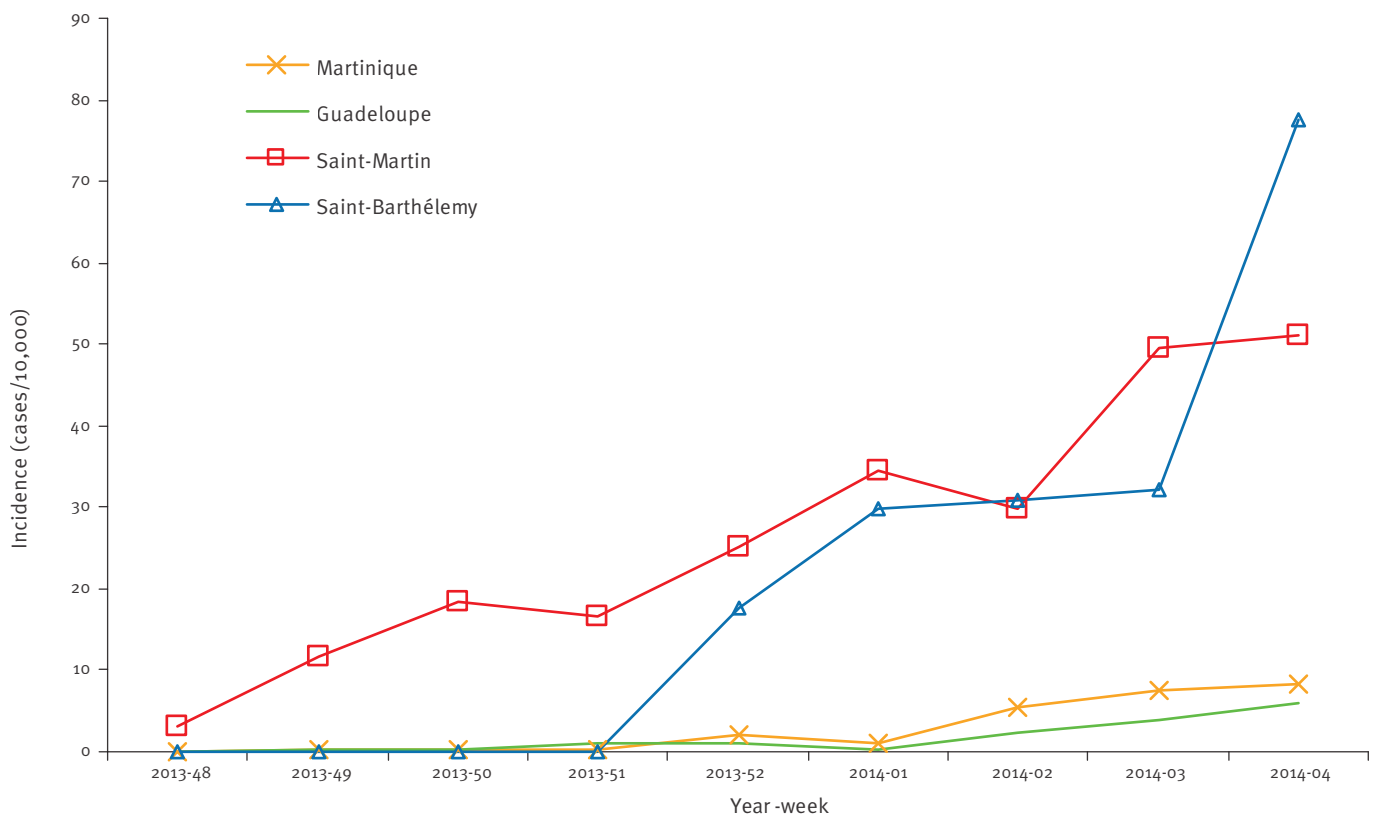
As of 27 March 2014, the estimated number of clinical suspected cases of chikungunya in Saint Martin was 2,750 and the number of confirmed cases was 784 (week 48 2013 to 12 2014). Three deaths indirectly related to chikungunya were reported.

A total of 435 clinical suspected cases were estimated on the island of Saint Barthélemy and 134 infections have been confirmed (week 50 2013 to 12 2014).

In Martinique, 9,340 clinical suspected cases of chikungunya were estimated (week 49 2013 to 12 2014) and 1,207 cases were identified as laboratory-confirmed

FIGURE 4

Weekly incidence of the estimated suspected cases of chikungunya by the sentinel network in Guadeloupe, Martinique, Saint Barthélemy and Saint Martin, 1 December 2013–26 January 2014



The period 1 December 2013–26 January 2014 corresponds to the weeks 48 2013–4 2014.

cases. Two deaths were reported in Martinique in hospitalised patients: one death was classified as indirectly linked with chikungunya; the second death is under investigation.

In Guadeloupe, a total of 2,270 clinical suspected cases were estimated to have occurred (week 52 2013 to 12 2014) and 734 cases were confirmed for the infection in this island (Figures 2 and 3).

A rapid increase of the weekly incidence was observed in the smaller islands Saint Martin (population: 36,029) and Saint Barthélemy (population: 9,035) compared to the larger islands Martinique (population: 392,290) and Guadeloupe (population: 404,640) (Figure 4).

Since the beginning of the outbreak, 11 cases from Saint Martin and Martinique were imported in French Guiana. The first autochthonous cases in French Guiana were reported on 19 February, with a total of 24 autochthonous laboratory-confirmed cases in week 11 2014.

In Saint Martin, all areas of the island have been affected by the virus, a predominant number of confirmed cases occurred in Sandy Ground, Concordia and

Quartier d'Orléans. In Martinique, the outbreak is geographically generalised. The main city, Fort-de-France, had the highest attack rate (estimated from the weekly number of notifications of clinical suspected cases) followed by, La Trinité, Case Pilote, Schoelcher, Saint-Pierre, and Les Anses d'Arlet. The main cluster identified in Guadeloupe was located in Baie-Mahault and in other municipalities of the windward shore of Basse Terre. In total, 27 of 32 municipalities had at least one confirmed case.

Microbiological investigation

Before the outbreak phase, laboratory confirmation was requested for every clinical suspected case of chikungunya. The diagnostic algorithm was intended to be followed by practitioners and microbiological laboratories. The samples were processed according to the date of the onset of symptoms and the date of sample collection. When the sample was taken between the first and fifth day after symptom onset, the sample was processed by RT-PCR. When the sample was taken between the fifth and the seventh day after symptoms onset, the sample was processed both by RT-PCR and detection of IgM and IgG, for the remainder only IgM and IgG detection was performed.

Because both dengue and chikungunya viruses are currently circulating, dengue diagnostic was systematically performed parallel to chikungunya laboratory tests. The microbiological analysis strategy was adapted according to the respective outbreak situation. In the territories where there was evidence of wide virus spread, only at-risk patients (when laboratory confirmation was needed to support the case management) and uncommon forms of the infection were targeted for laboratory confirmation (Martinique, Saint Barthélemy and Saint Martin, from week 5 2014). Local, regional and national capacities support the diagnostic strategy of the region (National Reference Laboratories and hospital-based microbiological laboratories).

On 10 December 2013, five days after the detection of the first autochthonous cases in Saint Martin, the complete chikungunya virus sequence showed that this virus belongs to the Asian genotype and the information was shared with the relevant public health authorities [13].

Control measures

All houses and work places of confirmed cases were targeted by vector control measures as scheduled in the Management, Surveillance and Alert of chikungunya outbreak Programme, which was implemented as a result of the outbreak. Epidemiological and entomological investigations were conducted simultaneously in the neighbouring environment of the suspected and confirmed cases (during pre-outbreak and outbreak phases) as well as interventions on the whole territory (outbreak phase), to identify possible clusters of cases and to implement vector control targeting adult mosquitoes and their breeding sites.

Public education was established through radio spots, television, distribution of flyers and posters with prevention messages in public areas, airports, private practitioner's offices, hospitals and clinics. The health authorities also implemented a specific programme preventing possible shortage of healthcare capacities due to the high burden of patients on emergency, hospital and outpatient capacities.

Overseas territories of the Netherlands

The overseas territories of the Netherlands in the Caribbean region comprise six islands grouped in three smaller Windward Islands in the north, and three larger Leeward Islands in the south, just north of the Venezuelan coast. The total population of these islands is 320,000 and ranges from 2,000 (Saba) to over 147,000 (Curaçao). The three islands with a larger population, Aruba, Curaçao, and Sint Maarten, are independent states within the Netherlands, the other three islands (Bonaire, Sint Eustatius and Saba), the so-called BES islands, have the status of special municipalities within the Netherlands. Sint Maarten (close to 40,000 inhabitants) is the southern part of the island of which the Northern part is formed by Saint Martin.

Epidemiological situation

The first report of laboratory-confirmed autochthonous chikungunya case in the overseas territories of the Netherlands was received by section General Public Health of the Department of Collective Prevention Services in Sint Maarten on 22 December 2013. The case had had onset of illness on 6 December 2013. Since the start of the outbreak, the total number of confirmed patients diagnosed with chikungunya on Sint Maarten has been 234 (up to week 11 2014), including one hospitalised case. The Dutch case definition for confirmed cases is fever ($>38.5^{\circ}\text{C}$) and joint pain in a person who has a positive polymerase chain reaction (PCR) and/or specific positive IgM antibody test. The proportion of test-positive samples increased from 29% (2/7) in December 2013 up to 69% (77/111) at the end of March 2014. The Caribbean Public Health Association (CARPHA) is, amongst other activities, assisting the countries and territories in the Caribbean region in the surveillance of communicable diseases. In this context they operate a syndromic surveillance system. Data from the surveillance showed for Sint Maarten an average and stable number of patients with undifferentiated fever since December 2013. Since the end of January 2014, start of week 5, the syndromic surveillance showed a consistently higher number of cases of undifferentiated fever compared to the historical average, generally below five cases per week based upon four years of data. Since week 5, cases vary between two and 34 per week (an average of 13 per week between week 5 and 12). Although there has been an ongoing dengue outbreak during this period, the increase is likely to be due to chikungunya, given that dengue season started well before January.

The number of confirmed cases on Sint Maarten ($n=234$) is much lower than on Saint Martin ($n=784$) although the number of inhabitants of both parts of the island is comparable (ca. 40,000). Because of intense traffic occurs between the two parts of the island and ecological barriers are absent, there is no obvious reason why the disease would be more prominent in the northern than in the southern part of this small island (87 km²). More likely, the difference in the number of reported cases is due to the difference in the availability of diagnostic testing and under-reporting. Twelve patients from Sint Maarten were diagnosed by general practitioners from Saint Martin. From the epidemiological data currently available, the residencies of most patients cannot be identified in a reliable manner.

The other two Dutch Windward islands, Saba and Sint Eustatius, have small populations (2,000 and 3,900) of which no patients have been diagnosed so far. The syndromic surveillance on these islands shows a low and stable number of patients with undifferentiated fever since December 2013. A rise in these figures could be an early signal for emergence of chikungunya. In the Dutch Leeward Islands, Aruba, Bonaire and Curaçao, no autochthonous cases have been identified so far. One imported confirmed case returning from Saint

Martin was reported on the island of Aruba in the first week of February 2014 (Figures 2 and 3).

Microbiological investigation

The first three patients from Sint Maarten were diagnosed by the French National reference laboratory (CNR-IRBA Marseille) using RT-PCR testing. On January 2014, serum samples from Sint Maarten were sent to the virological laboratory of the National Institute for Public Health and the environment (RIVM) in Bilthoven, which made diagnostic testing available. Reference materials were obtained from the laboratory in Marseille (CNR-IRBA). Due to a lack of information about the date of onset of illness, all samples were tested by RT-PCR and for chikungunya-specific IgM and IgG-antibodies when RT-PCR was negative. Because transport of samples is both expensive and time consuming, the RIVM assists the local laboratories of Sint Maarten and Curaçao to implement serological testing indirect fluorescent-antibody (IFA) from the second quarter of 2014.

Control measures

Mosquito control services are present on Sint Maarten and routine measures are the same as for the control of dengue fever: fogging with adulticides (Evolver 4-4; active ingredient: permethrin/piperonyl butoxide), removal of breeding sites, application of larvicides in water containers and health education on prevention of mosquito bites. Upon arrival, tourists, which are paramount for the regional economy of the islands, are informed of the ongoing outbreak of chikungunya and advised to take personal protection measures against mosquito bites. The local authorities make use of the preparedness and response plan of the United States (US) Centers for Disease Control and Prevention (CDC) for introduction of chikungunya virus in the Americas, which was introduced during two workshops in 2012 hosted by Pan American Health Organization (PAHO) [14]. Specialists from the CARPHA and the PAHO have provided expert advice concerning control in January 2014 by means of a work visit to Sint Maarten. General practitioners have been informed of the presence of the disease and an intensified surveillance has been initiated by the Public Health Authority of Sint Maarten. The ministry of Health has initiated procedures in order to make chikungunya cases notifiable for the BES islands. General practitioners and specialists on all other overseas territories in the Netherlands have been informed of this emerging epidemic, and have been advised concerning diagnostic testing since the end of December 2013.

Overseas territories of the United Kingdom

The overseas territories of the United Kingdom (UK) in the Caribbean region comprise five territories of which three (Anguilla, British Virgin Islands and Montserrat) are located within the Lesser Antilles east of Puerto Rico and two (Cayman Islands and Turks and Caicos Islands) in the western Caribbean in the Greater Antilles. The total population of these territories is around 136,000 and ranges from just over 5,000 (Montserrat) to around

53,200 (Cayman Islands). All are internally self-governing UK overseas territories.

A standard case reporting form is used to collect information on chikungunya cases (based on the case definition). Reports from undifferentiated fever ($>38.5^{\circ}\text{C}$), which might include chikungunya cases, are collected on a weekly basis from sentinel sites.

Epidemiological situation

British Virgin Islands: three cases of chikungunya were confirmed by CAPHA on Jost Van Dyke island in the British Virgin Islands on 13 January 2014 (Figures 2 and 3). The cases had onset of symptoms on the 15, 17 and 25 December 2013. The symptom profile of the three cases consisted of fever ($>38.5^{\circ}\text{C}$) and severe arthralgia. Retro-orbital pain, back pain, and rash were not present. There was no history of travel. These three cases tested positive for chikungunya and were negative for dengue by PCR. As of 27 March 2014, a total of seven autochthonous cases have been confirmed in the British Virgin Islands, all from Jost Van Dyke island; the most recent case with onset of illness on 5 February 2014 (week 6 2014).

Anguilla: On 31 January 2014, one case of chikungunya, believed to be imported from Saint Martin was diagnosed in Anguilla and confirmed by CARPHA in Trinidad. As of 27 March, a total of 14 confirmed cases (13 autochthonous and one imported) have been reported in Anguilla with onsets of illness between 27 January and 16 February 2014.

The case definition used is in line with the one provided by CARPHA: a suspected case is a patient with acute onset of fever $>38.5^{\circ}\text{C}$ and severe arthralgia or arthritis not explained by other medical conditions, and who resides or has visited epidemic or endemic areas within two weeks prior to the onset of symptoms; a probable case is defined as a suspected case with a positive result for chikungunya by IgM enzyme-linked immunosorbent assay (ELISA); and a confirmed case is a suspected case with a positive result for chikungunya by viral isolation, RT-PCR or four-fold increase in chikungunya virus specific antibody titres (samples collected at least 2 to 3 weeks apart).

Microbiological investigation

Molecular PCR testing for chikungunya is undertaken by CARPHA in Trinidad and the first positive samples in British Virgin Islands were sent to the US CDC for verification, as these were the first cases confirmed by the Trinidad laboratory.

Control measures

The vector control unit of the Environmental Health Division of the British Virgin Islands performed control activities and monitoring as well as house to house inspections and education at the time of the initial reports. They have been monitoring mosquito indices on Jost Van Dyke. Surveillance activities have

been increased. The Ministry of Health and Social Development in Anguilla continues to work in collaboration with the relevant agencies to ensure that the appropriate preventative measures are implemented to reduce and contain the spread of the virus. Measures include mass education of the public to raise awareness of symptoms and prevention, fogging in areas where confirmed or suspected cases of chikungunya have been reported and engaging with port health teams at sea and airports in order to implement appropriate controls.

Discussion

Chikungunya is endemic in Africa, south-east Asia and on the Indian subcontinent with outbreaks occurring beyond the well-known endemic areas from 2005 (Figure 1). Compared to this historical occurrence, this is the first documented outbreak of chikungunya in the Americas. The virus in the Caribbean belongs to the Asian genotype [13]. It might have been introduced by travellers from Asia where outbreaks were reported in 2013. With the increased transmission of chikungunya in Asia and Africa in the last decade, the Caribbean region has been considered highly vulnerable [14]. The primary vector, *Ae. aegypti*, is widespread in the region [15], but also *Ae. albopictus* is found in the Americas and on a number of Caribbean islands [16]. The latter species has not been found in French Guiana, the French Caribbean islands nor the Dutch Caribbean territories but the climate suitability model revealed that the area is highly suitable for this vector species [15-17]. The presence of a human population naïve to the chikungunya virus, competent vectors in the region and the intense movement of people into and between islands are factors that most likely contributed to the extension of the virus circulation. Indeed, contacts between the islands are high as exemplified by the increased traffic between Saint Martin/Sint Maarten and the British Virgin Islands as a consequence of a boat show in the British Virgin Islands in December 2013. Besides the reported affected areas of the French, Dutch and British overseas territories, confirmed cases were reported from Dominica and Saint Kitts and Nevis (Figure 3 and [18,19]) and the first autochthonous transmission on the continent was confirmed in French Guiana 11 weeks after the first confirmed case on Saint Martin (week 8 2014). The establishment of autochthonous transmission following importation of viraemic patients in other territories of the Americas is expected and will likely have a significant public health impact in the region. Surveillance in the region, which is well established for dengue, has been intensified and laboratory testing has been strengthened in collaboration with regional or international reference laboratories. Further, a close follow-up of the situation and co-ordinated surveillance and control within the regions is still needed.

The vulnerability of Europe for the transmission of chikungunya virus and other arboviruses was recognised prior to 2007 [20] and confirmed with the first chikungunya outbreak in Italy in 2007 [8,21,22]. For onward

transmission to occur, the introduction of this virus into Europe would need to coincide with high vector abundance and activity i.e. during the summer season in the EU. Hence, chikungunya outbreaks in the northern hemisphere are of bigger concern for the EU than those in the southern hemisphere [23]. During the period from 2008 to 2012, 475 imported chikungunya cases have been reported by 22 EU/European Economic Area (EEA) countries [7]. Most cases originated from Asia (one third from India, otherwise Indonesia, Maldives, Sri Lanka and Thailand) and Africa (including islands from the Indian Ocean). Temporal clusters of chikungunya cases imported in the EU are largely synchronous with large outbreaks in endemic countries as reported for Germany [24]. The occurrence and possible establishment of chikungunya in the Caribbean region adds an additional possible source of introduction of the virus. Because of the relatively intensive traffic between the overseas territories and the EU, introduction of chikungunya in Europe can be anticipated and blood safety measures could be considered [25]. It should be noted that both autochthonous dengue cases in France in 2010 and 2013 followed the introduction of a viraemic patient from the French Caribbean overseas territories. The introduction of chikungunya viraemic persons will most likely not lead to onwards transmission in Europe during the winter season as the vectors are not active during this season. However, vigilance is needed if the outbreak in the Caribbean region continues and overlaps with the mosquito vector season in areas where *Ae. albopictus* is established in continental Europe.

Firstly reported in Europe in 1979 in Albania [26], the mosquito vector *Ae. albopictus* has continuously expanded its distribution in the EU. To date this species has colonised almost all Mediterranean countries and has been found introduced, without establishment in Austria, Belgium, Czech Republic, in more northern localities in France, and the Netherlands, [10]. *Ae. albopictus* can reach high densities from July to September around the Mediterranean where it is established [27]. *Ae. aegypti* has recently established on Madeira and is found around the Black Sea coast. The A226V mutation of ECSA chikungunya virus has increased the transmissibility of the chikungunya virus by *Ae. albopictus* [11] and vector competence studies using *Ae. albopictus* populations from France showed that both the mutated and non-mutated ECSA chikungunya strains can be transmitted by local mosquito populations [28]. The chikungunya strain currently circulating in the Caribbean region does not belong to the ECSA genotype but to the Asian genotype. The strain is related to strains recently identified in Indonesia, China and the Philippines [13]. The competence of the European population of *Ae. albopictus* to transmit this chikungunya strain needs investigation.

In conclusion, spread and establishment of the disease in the Caribbean and other regions in the Americas can be anticipated given the high connectivity between the affected and non-affected areas and the widespread

occurrence of efficient vectors. Also, the risk of introduction of the disease to the EU from the affected territories in the Caribbean should be considered especially in the context of the next mosquito season in Europe. Clinicians should be aware that, besides dengue, chikungunya should be considered among travellers currently returning from the Caribbean region. The clinical picture of both infections can be similar and might be a challenge for clinicians that are not familiar with the clinical presentation of these infections.

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Conflict of interest

None declared.

Authors' contributions

Wim Van Bortel coordinated and drafted the manuscript, and reviewed final document for accuracy; Frédérique Dorleans coordinated and drafted the part of the manuscript on the French Caribbean territories and reviewed the different versions of the MS / Permanent member of the outbreak team management in Martinique; Jacques Rosine and Alain Blateau are permanent members of the outbreak management team in Martinique and permanent member of the regional outbreak management team (French Caribbean territories) and responsible for the data collection management and interpretation; Dominique Rousset form the French National Reference Center for Arboviruses is head of the associated lab for the French departments of the Americas and involved in virological diagnosis and manuscript proofreading; Fatiha Najjioullah of the University Hospital Laboratory of virology, Fort-de-France, Martinique manages the molecular virological diagnosis and in involved in virological diagnosis and manuscript proofreading ; Raymond Césaire Head of the virology laboratory of the University Hospital Laboratory of virology, Fort-de-France, Martinique was involved in the implementation of virological diagnosis; Séverine Matheus of the French National Reference Center for Arboviruses is deputy head of the associated laboratory for the French departments of the Americas and involved in virological diagnosis and manuscript proofreading; Isabelle Leparç-Goffart Head of the French National Reference Center for Arboviruses and coordinating all French territories is involved in virological diagnosis and participated to the writing of the manuscript; Olivier Flusin of the French National Reference Center for Arboviruses, is involved in virological diagnosis and editing of the manuscript; Christine M Prat of the French National Reference Center for Arboviruses is involved in virological diagnosis and editing of the manuscript; Vanessa Ardillon is a permanent member of the outbreak management team in French Guyana and member of the regional outbreak management team (French Caribbean territories) and responsible

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Local and regional spread of chikungunya fever in the Americas

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Chikungunya fever (CHIKV), a viral disease transmitted by mosquitoes, is currently affecting several areas in the Caribbean. The vector is found in the Americas from southern Florida to Brazil, and the Caribbean is a highly connected region in terms of population movements. There is therefore a significant risk for the epidemic to quickly expand to a wide area in the Americas. Here, we describe the spread of CHIKV in the first three areas to report cases and between areas in the region. Local transmission of CHIKV in the Caribbean is very effective, the mean number of cases generated by a human case ranging from two to four. There is a strong spatial signature in the regional epidemic, with the risk of transmission between areas estimated to be inversely proportional to the distance rather than driven by air transportation. So far, this simple distance-based model has successfully predicted observed patterns of spread. The spatial structure allows ranking areas according to their risk of invasion. This characterisation may help national and international agencies to optimise resource allocation for monitoring and control and encourage areas with elevated risks to act.

Introduction

Chikungunya fever is caused by the chikungunya virus, an alphavirus that is transmitted by several species of mosquitoes, including *Aedes albopictus* and *Ae. aegypti* [1]. In the last decade, large outbreaks of chikungunya fever have been reported in the Indian Ocean region [2], with millions of people experiencing incapacitating arthralgia, fever and rashes [3,4]. Transmission was sustained even in places with high standards of sanitary organisation [5].

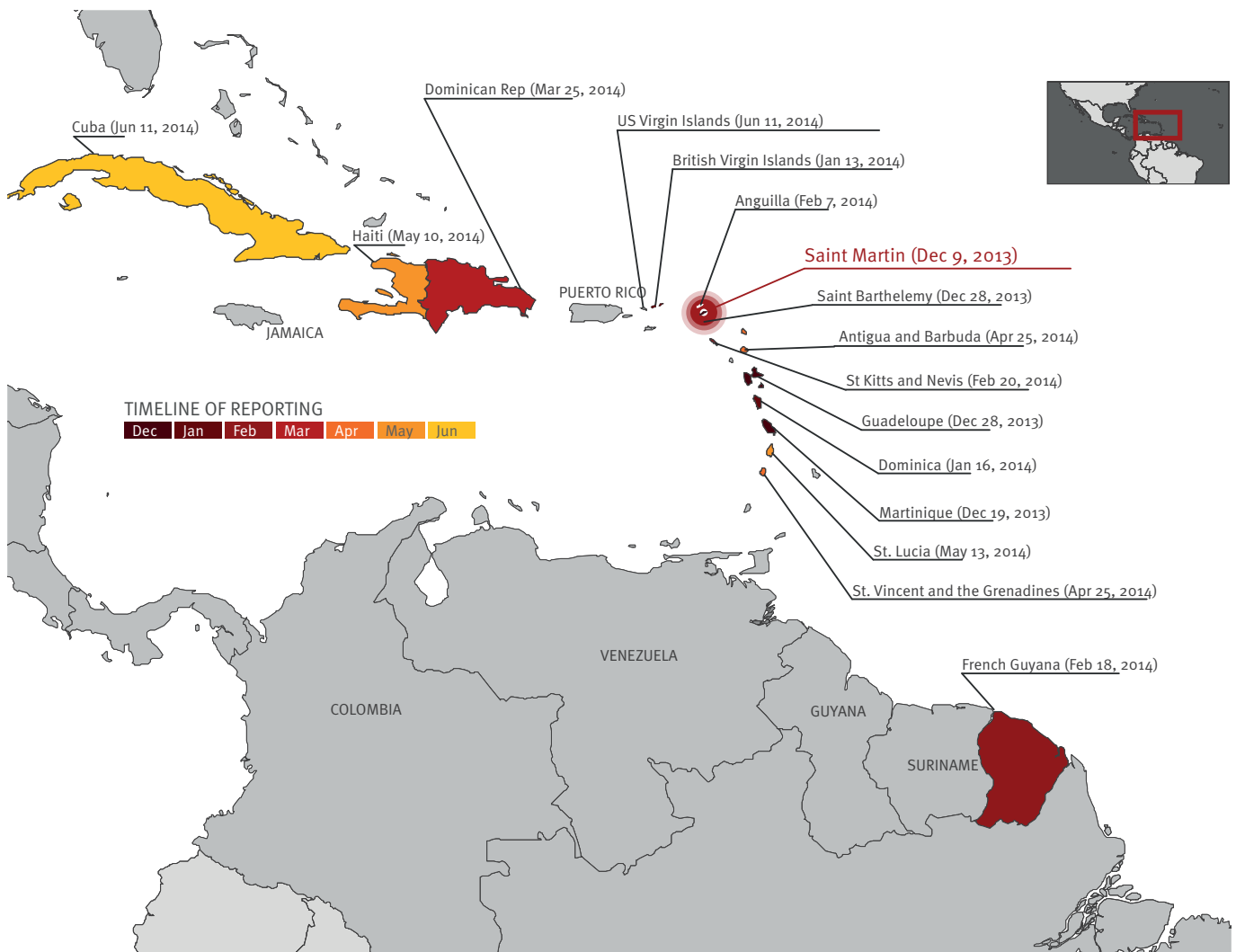
An outbreak of chikungunya fever is currently affecting an increasing number of areas in the Caribbean [6-8]. Figure 1 shows areas that reported at least one autochthonous case by 15 June 2014. The figure also shows the timeline of reporting. The first area reporting cases was Saint Martin (9 December 2013) with symptom onset of the first documented case on 5 October 2013. Further reports quickly followed from two other French territories, Martinique on 19 December 2013 and Guadeloupe on 28 December 2013. By 15 June 2014, 16 areas had reported at least one autochthonous case.

This rapid expansion constitutes a source of concern for public health in the Americas [8]. The mosquito vector is found in a wide geographical zone that goes from South Florida to Brazil [10]. The potential for geographical expansion is therefore considerable and extends far beyond the areas currently affected. Moreover, the Caribbean is a highly connected area with frequent exchanges among the islands in the region, with mainland America and with Europe: more than 10 million international visits are reported each year by the World Tourism Organization, including 25% from Europe [11]. These important connections increase the risk of the current epidemic expanding quickly to a wider area in the Americas. Furthermore, the epidemic generates importations of cases into Europe, where the mosquito species *Ae. albopictus* is well established in many countries, primarily around the Mediterranean [9,12]. As of 1 July 2014, 98 imported laboratory-confirmed cases have been reported for metropolitan France alone [13].

In order to support preparedness and response planning in affected areas and those at risk of invasion (i.e. arrival of the disease in the area), it is important that we understand better the local and regional

FIGURE 1

Chikungunya fever in the Caribbean, as of 15 June 2014



Areas that reported at least one laboratory-confirmed autochthonous case of chikungunya fever are coloured according to the timeline of reporting [6]. The first date of symptom onset was 5 October 2013, on Saint Martin.

Box

List of areas included in the assessment of chikungunya virus transmission (n=40)

Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, British Virgin Islands, Cayman Islands, Colombia, Costa Rica, Cuba, Curacao, Dominica, Dominican Republic, El Salvador, Florida, French Guiana, Grenada, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Netherlands Antilles, Nicaragua, Panama, Puerto Rico, Saint Barthelemy, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Turks and Caicos Islands, United States Virgin Islands, Venezuela.

dynamics of spread of chikungunya fever in the Caribbean. Firstly, how effective is transmission of the disease in the Caribbean? Answering this question is important to assess the potential for large and explosive outbreaks as seen previously in the Indian Ocean region. Secondly, we need to understand the regional dynamics of spread and their determinants to assess which areas currently are at risk of invasion, to help national and international agencies with resource allocation, technical support and planning, and to encourage areas with elevated risks to act. This is essential in order to reduce disease burden in the Americas, but also to reduce the number of imported cases in Europe.

Here, we provide the first assessment of the effectiveness of transmission of the virus in the Caribbean and of the factors explaining the spread at the regional level.

Methods

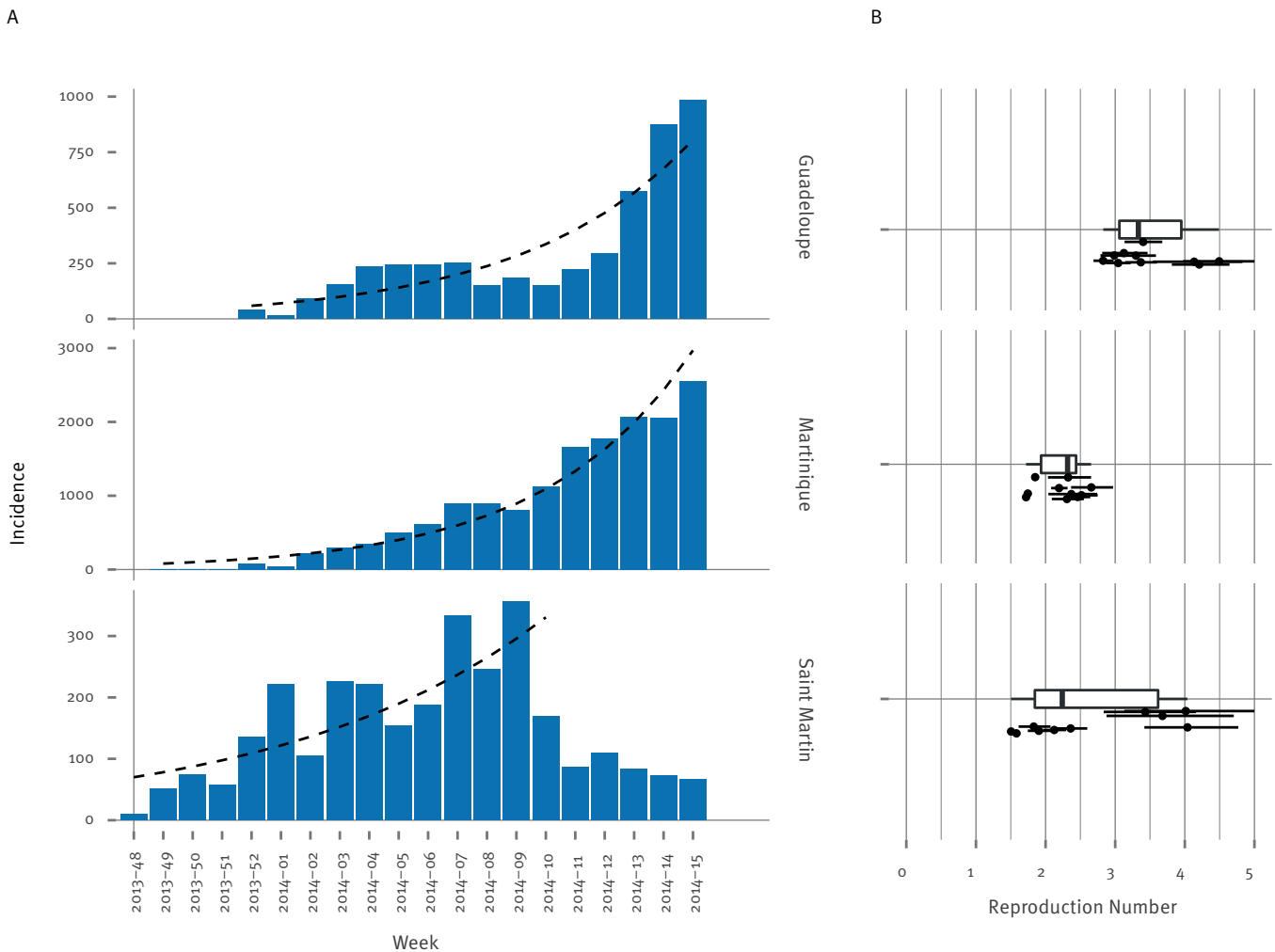
Data collection

We selected 40 areas (countries or territories) around the Caribbean which overlap with areas infested by *Ae. aegypti* mosquito [10] and where dengue is present [14,15] in central America (Box).

We defined areas officially affected by chikungunya fever as those reported to have had at least one laboratory-confirmed autochthonous case of chikungunya fever in the ProMED-mail alerts [6], the Pan American Health Organization [16] or the Caribbean Public Health Agency [17]. The date of the first report was also recorded.

In the French overseas territories (Saint Martin, Martinique and Guadeloupe), detailed data were collected by Cire Antilles-Guyane, using different approaches as the health authorities adapted to the situation. At first, an investigation was started around suspected or clinical cases with retrospective identification of other suspected cases in the neighbourhood. Virological confirmation was undertaken for most of the clinically suspected cases by the two laboratories of the national reference centre (Marseille and Cayenne). As the number of cases increased, existing surveillance networks based on general practitioners (GP) were asked to monitor clinical cases according to the case definition (patient with onset of acute fever >38.5 °C and severe arthralgia of hands or feet not explained by another medical condition). The surveillance network comprised 100% of the GPs on Saint Martin (15

FIGURE 2
Reproduction number of chikungunya fever in the Caribbean, 2014

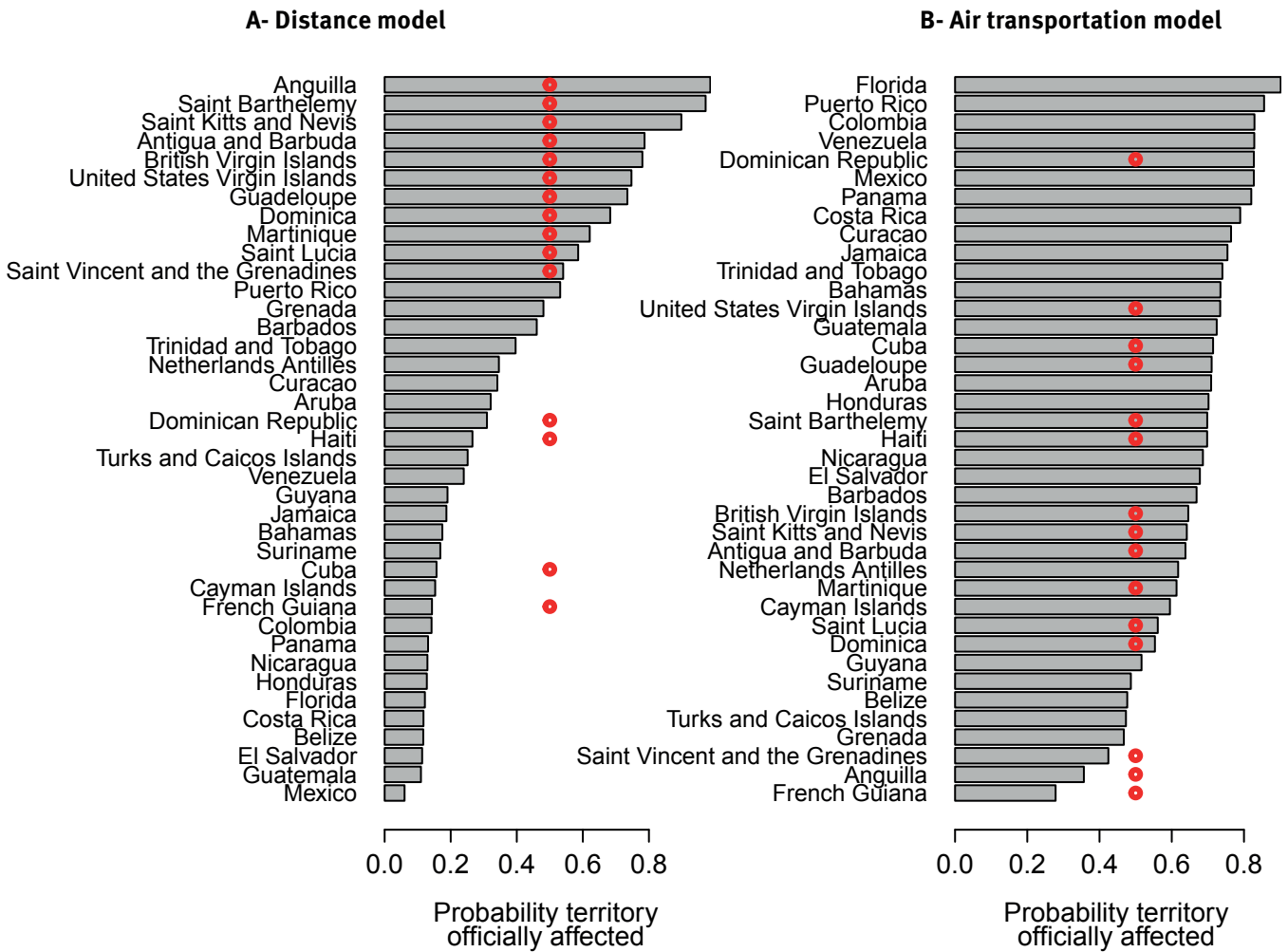


A Epidemic curves based on clinical surveillance systems in general practice on three French islands (bars). An exponential fit to the whole epidemic is shown as a dashed line.

B. Estimates of the reproduction number based on the exponential growth for the 10 time periods of four weeks or more with the best fits. The boxplots show the median, interquartile interval and range of the 10 point estimates.

FIGURE 3

Areas in the Caribbean officially affected by chikungunya fever on 15 June 2014 and prediction in the distance model (A) and the air transportation model (B)



The grey bars give the probability predicted by the model that the area should be officially affected by 15 June 2014, sorted in decreasing order. The red dots indicate areas that were officially affected by 15 June 2014 according to the data. A good fit is suggested when most of the red dots appear at the top of the pyramid.

of 15) and around 20% on Martinique and Guadeloupe. Virological confirmation was no longer systematically undertaken as the number of cases increased.

Commercial air connections and 2013 data for volume of passengers between airports of the region were obtained from the International Air Transport Association [18,19]. These data correctly captured multi-leg flight trajectories, i.e. if a person flew from Florida to Jamaica via Puerto Rico, the recorded itinerary would be the Florida to Jamaica journey. Distances between the centroids of the areas were computed.

Characterising local transmission on Saint Martin, Martinique and Guadeloupe

The human-to-human initial reproduction number *R* (mean number of secondary cases generated by a human case) was computed using the exponential

growth method [20]. We explored the variability of these estimates by analysing all time periods of four weeks or more in the epidemic curves and reporting the 10 periods for which our exponential growth model had the best fit to the data (as measured by the deviance *R*-squared statistic [21]). Additional details can be found in the supplementary material* that can be accessed at <https://docs.google.com/file/d/oBopDXBmlKKGMRW9ucWRpaVV5bDQ/edit?pli=1>.

Characterising regional spread

The transmission paths between areas were analysed under the hypotheses that the risk of invasion arose from previously invaded areas with data available as of 15 June 2014 [22]. We considered that Saint-Martin was the first invaded territory, with a first case on 5 October 2013. For other areas, a delay of on average 30 days

was allowed between invasion and reporting. Different mathematical models were developed in which the instantaneous risk of transmission between areas depended on population size, distance, air traffic volume or a combination thereof. The models were fitted by Markov chain Monte Carlo sampling [23]. Goodness of fit was assessed by determining how well the models agreed with the set of areas officially affected by the time the analysis was performed. Finally, we used the best model to predict areas with the highest risk of invasion. As we have been using this model since early 2014, we also evaluated retrospectively short-term predictions that were made with data available on 15 January 2014 and on 30 March 2014. Technical details are available in the supplementary material*.

Results

Local transmission on Saint Martin, Martinique and Guadeloupe

Surveillance of clinically suspected cases started in weeks 48, 49 and 52 of 2013 on Saint Martin, Martinique and Guadeloupe, respectively. The fit of an exponential increase to the first weeks of each outbreak was

reasonable, leading to estimates of the reproduction number in the range 2 to 4 (Figure 2). The reproduction number was estimated to be slightly higher on Guadeloupe than on Martinique, due to a renewed outbreak starting in week 10 of 2014 on Guadeloupe.

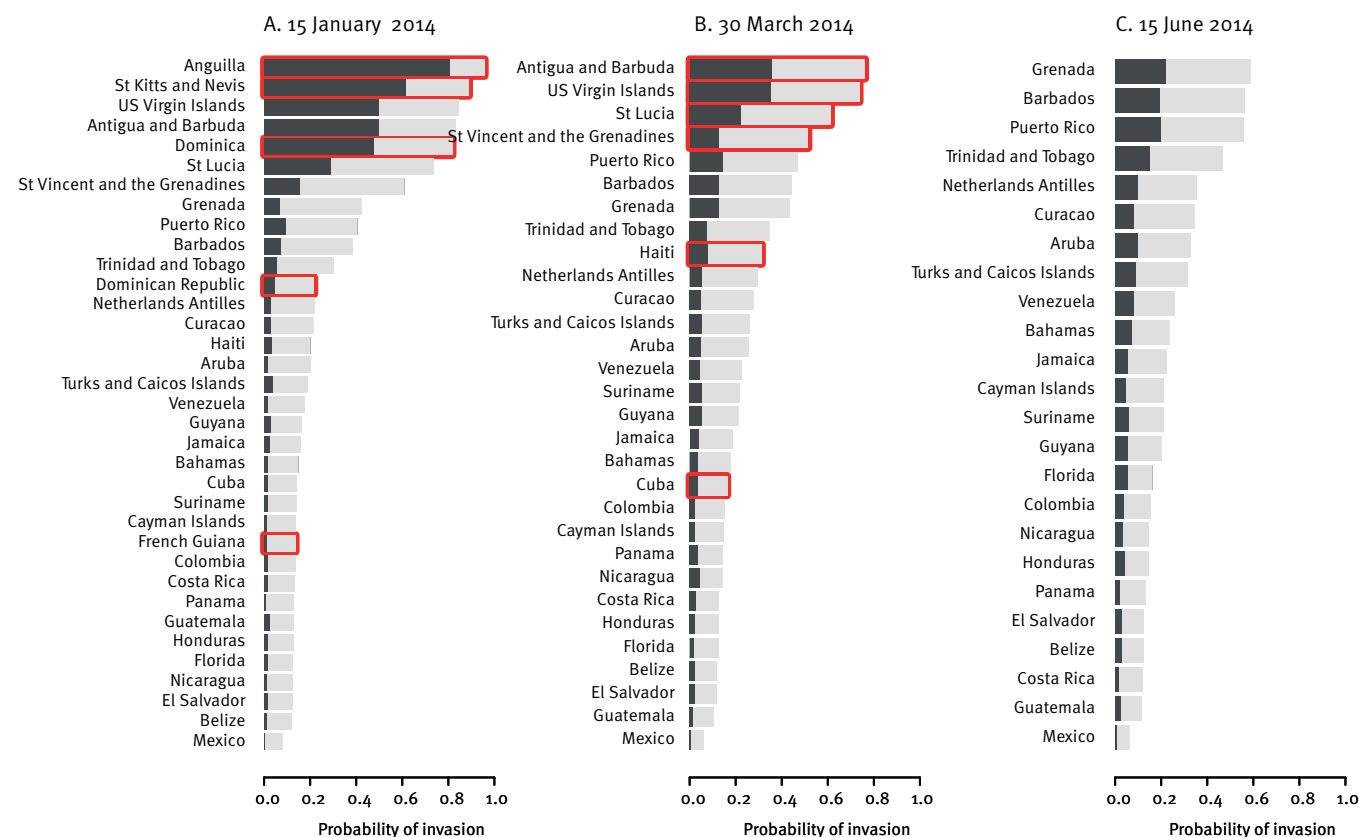
Regional spread

A marked geographical pattern of the spread was apparent (Figure 1), as 12 of 16 officially affected areas were situated in a relatively small geographical zone between the British Virgin Islands in the north-west and Saint Vincent and the Grenadines in the south-east.

We found that this pattern was best explained by making the risk of transmission between areas inversely proportional to distance. If we exclude the seed location Saint Martin, 15 areas were officially affected. Of these 15, 11 were at the top of the list of areas predicted to be at highest risk of invasion by this simple model based on distance (Figure 3A). In contrast, only one of 15 officially affected areas was at the top of the list if the risk of transmission was instead assumed to depend on air passenger flows, indicating that air passenger flow was a poor predictor of transmission

FIGURE 4

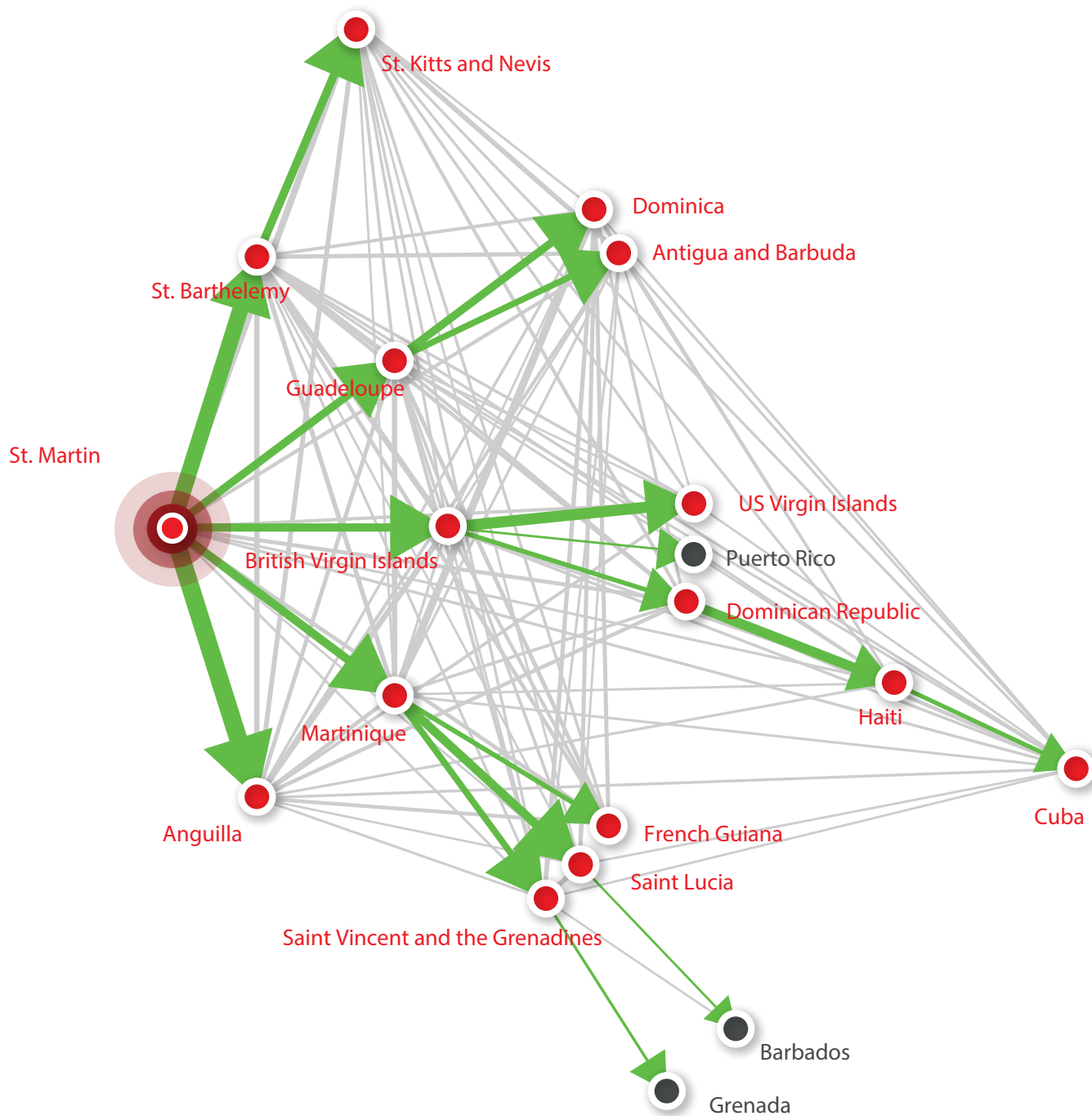
Short-term predictions of the distance model performed on different dates in the chikungunya fever epidemic in the Caribbean with data as available on these dates



Dark bars indicate the probability of areas already invaded at the time the analysis was performed. Light bars give the probability that the area would be invaded in the 75 days following the time of the analysis. For analyses performed on 15 January and 15 June 2014, we highlight in red the areas that became officially affected in the 75 days following the date of analysis.

FIGURE 5

Most probable source of transmission for areas that are officially affected by chikungunya fever and for those that may already be invaded but have not yet reported cases



Transmission tree for areas officially affected (in red) and for those that have at least 20% probability of already being invaded (in grey). The transmission tree is visualised in a topological space where areas are organised in successive layers starting from Saint Martin according to their most probable source of transmission. Most probable transmission links are plotted in green; other links with probability larger than 3% are plotted in grey. The thicker the arrow, the higher the probability of transmission.

(Figure 3B). Population sizes of areas were not found to significantly affect transmission (see supplementary material*).

Figure 4 presents predictions made with this model on 15 January 2014 (Figure 4A) and on 30 March 2014 (Figure 4B). It shows the risk of being already invaded at the time of the analysis or of being invaded in the following 75 days, based on data available at the time. Overall, performance of the model has been good, as most areas officially affected in the following 75 days were among those that had the highest predicted risk of invasion. Of 11 areas officially affected during this period, French Guiana and Cuba were the only two with low predicted risks.

Figure 4C shows predictions of the model with data available on 15 June 2014. Grenada, Barbados and Puerto Rico currently have the largest predicted probability of being invaded in the 75 days following the analysis (36%). We note that heterogeneity in the predicted risk of invasion has decreased as Chikungunya has expanded in the region, with the standard deviation in the predicted risk declining from 27% on 15 January 2014 to 15% on 15 June 2014.

Assuming that Saint Martin was the seed of infection in the region, Figure 5 shows the most likely path of transmission for areas that were either officially affected or likely to be already invaded although autochthonous cases had not been reported. The first round of invasion included Martinique, Guadeloupe, Saint Barthélemy, British Virgin Islands and Anguilla. The second round of invasion eventually led to eight new invaded areas, including Dominica and French Guiana. Four rounds were necessary for the disease to reach Cuba. Looking at the reconstructed transmission tree and restricting the analysis to areas that were officially affected, we found that the median distance between two areas predicted to have transmitted chikungunya to each other was 476 km (95% CI: 16–2,040). It was 173 km (95% CI: 16–451) and 626 km (95% CI: 54–2,043), respectively, for areas in the first and in subsequent rounds of the regional epidemic.

Discussion

The chikungunya virus has found a propitious environment for transmission in the Caribbean. All areas of the Caribbean and Central America are at risk of invasion, although with important heterogeneities in their predicted risks. Our analysis provides a quantitative basis for informed policy making and planning.

Transmission of chikungunya fever was consistently estimated to be effective in the three French territories that first reported cases (Saint Martin, Martinique and Guadeloupe). Estimates of the reproduction number R ranged from 2 to 4, similar to what was reported in the Indian Ocean region [5,24], making large and fast-growing outbreaks possible. With the largest estimate, Guadeloupe may end up with the largest attack rate if

transmission goes on unchanged. Interestingly, incidence there showed sustained increase only after the epidemic entered the largest city (Pointe à Pitre), suggesting heterogeneity in transmission. In Saint Martin, incidence has notably slowed down in the last weeks, despite large growth at first. Further investigation is required to find out how vector abundance, heterogeneity in population mixing and exposure explain these outcomes. These estimates of R were obtained under the assumption that the serial interval was 23 days (see supplementary material*). Using a shorter duration for the gonotrophic cycle (three days vs four days) led to little change in the serial interval distribution (two days) and less than 5% variation on the estimates of R . With higher daily mortality in mosquitoes (15% instead of 10%), the serial interval was shorter, and the estimates of R were reduced by ca 20%.

Sustained transmission in the French islands has been in contrast with the limited number or absence of cases reported in some nearby areas. This could partly be explained if French territories were invaded first so that they had more time to build up large numbers of cases. However, heterogeneity in reporting is also likely to be involved, as some areas only reported the disease when it had already been responsible for hundreds of cases.

Indeed, a difficulty in the analysis of the regional diffusion of chikungunya fever has been the imperfect documentation of areas that were affected and of the dates when they were invaded. This is due to variable delays between (unobserved) dates of invasion and reporting of the first autochthonous cases. We did not model heterogeneities in the capabilities of the different areas to identify cases, as supporting data are lacking and this would therefore have been mostly subjective and added uncertainty to the analysis. But we used state-of-the-art data augmentation techniques [25-27] to overcome uncertainty about timing. In our baseline scenario, we assumed an average 30-day reporting delay but analysed alternative scenarios with shorter and longer delays in the supplementary material*. Reducing the reporting delay did not change the relative order of areas by risk of invasion but led to reduced probabilities of invasion in the near future. Unfortunately, we did not have independent data to back up the baseline assumption of an average 30-day delay in reporting.

To understand and predict regional spread, we postulated that importation of infected humans or mosquitoes by usual transportation routes was likely to be responsible for invasion of new areas. Most islands are served by air carriers, but travelling by boat, ferries and cruisers is also very common. Up to now, areas officially affected by chikungunya fever have presented smaller air passenger flows than those not yet affected (daily average: 797 as opposed to 2,476). It is therefore not surprising that air transportation data could not reproduce the patterns of spread seen so far

(Figure 3B). A direct assessment of alternative modes of transportation, including boats and cruises, was not possible due to a lack of detailed data on these routes. To overcome this limitation, we used standard geographical models where connections between areas depend on distance and population sizes [28-30]. We found that the spatial structure of the epidemic was most consistent with a model in which the strength of a connection was inversely proportional to the distance. Overall, our results suggest that short-range transportation such as boats and cruises hopping between islands are likely to have played a substantial role in the spread observed in the early phase of the chikungunya outbreak in the Caribbean.

The good fit of this distance model to current data (Figure 3A) and its successful predictions so far (Figure 4, panels A and B) give us some confidence in the short-term predictions of this model (Figure 4C). However, the relative importance of the transmission routes may change as the epidemic spreads, which could increase the risk to more distant areas in the longer term. In that respect, we note an apparent increase in the median distance of transmission between the first and subsequent waves in the regional epidemic. Given the current absence of correlation between available long-range air transportation data and disease spread, long-term predictions for international spread are harder to make.

The propensity of an area to get invaded and to transmit is expected to depend on vector activity and case numbers, respectively. Here, we used qualitative data on the presence of the *Ae. aegypti* mosquito [10], which are supported by recent reports on dengue virus circulation [14,15], to characterise vector activity. The vector was present in all areas included in our analysis [10,14,15]. Due to the lack of adequate data, we were unable to modulate the risk of invasion with more quantitative indicators of vector activity. Efforts to construct quantitative maps of vector activity should be a priority to improve model predictions. If they become available, data on incidence of cases in the invaded areas may improve the fit further, although this was not shown to be the case in the spatial analysis of other outbreaks [22]. Despite these limitations, short-term predictions of the model have been good (Figure 4, panels A and B). Improved predictions may require taking seasonality into account, as vector abundance may change with the seasons. The range of temperature is limited in the Caribbean islands (between 26 °C and 29 °C in Saint Martin), but larger changes are expected as we move away from the equator. Seasonal changes in the number of passengers to and from the Caribbean must also be considered when studying the risk of importation to Europe.

In conclusion, we have shown that chikungunya fever is an important threat in the Americas. The high transmissibility may lead to fast-growing and large outbreaks. Regional dissemination is under way, so far

with a simple geographical pattern, which is relevant for optimising the monitoring of areas.

*Note:

Supplementary information made available by the authors on an independent website is not edited by Eurosurveillance, and Eurosurveillance is not responsible for the content. The material can be accessed at: <https://docs.google.com/file/d/oBopDXBmlKKGMRW9ucWRpaVV5bDQ/edit?pli=1>.

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Conflict of interest

None declared.

Authors' contributions

ML, PQ, HDV provided the data. SC, CP, VC, PYB analysed the data. SC and PYB designed the analysis and wrote the first draft. All authors edited and commented the paper.

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Two cases of Zika fever imported from French Polynesia to Japan, December 2013 to January 2014

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We present two cases of imported Zika fever to Japan, in travellers returning from French Polynesia, where an outbreak due to Zika virus (ZIKV) is ongoing since week 41 of 2013. This report serves to raise awareness among healthcare professionals, that the differential diagnosis of febrile and subfebrile patients with rash should include ZIKV infection, especially in patients returning from areas affected by this virus.

We report two cases of Zika fever in Japan, which were imported from French Polynesia, where on 6 November 2013 public health authorities reported an outbreak of subfebrile illness with rash due to Zika virus (ZIKV). The epidemic started spreading across the archipelago beginning in week 41 of 2013 [1]. During weeks 42 to 52, the syndromic surveillance network reported 6,630 suspected ZIKV infection cases to the Bureau de Veille Sanitaire. About 500 of these cases were tested at the Institute Louis Malarde laboratory in Papeete for confirmation; 333 were confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) as ZIKV infections [2]. The outbreak is currently ongoing and as of 13 January 2014, 361 laboratory-confirmed

cases have been reported [3]. Symptoms of most ZIKV infection cases are mild and self-limited (mean duration of symptoms is 3–6 days). No hospitalisations for acute infection have been reported.

Case 1

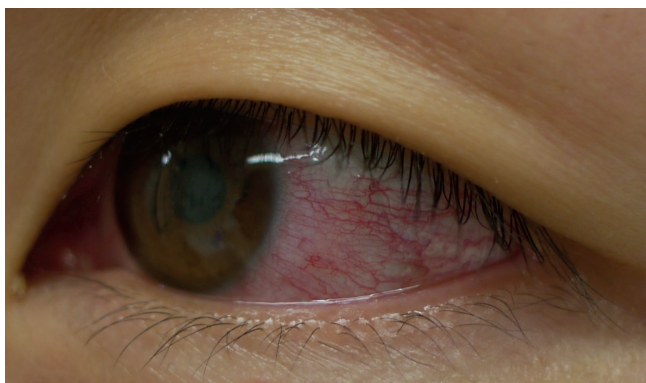
A previously healthy Japanese man in his mid-20s presented to our hospital in mid-December 2013 after four days of fever (self-reported), headache, and arthralgia and one day of rash. He had visited Bora Bora in French Polynesia, in the first week of December 2013 for six days for sightseeing with his partner. He did not use insect repellent during the trip. Upon examination, his body temperature was 37.2°C (99°F) and he had maculopapular rash on his face, trunk, and extremities. Other clinical examination results were normal. Laboratory tests revealed leucopenia ($3,300 \times 10^6/L$; norm: $3,500-8,500 \times 10^6/L$) and thrombocytopenia ($14,900 \times 10^6/L$; norm: $15,000-35,000 \times 10^6/L$). ZIKV RNA was detected in serum using real-time RT-PCR performed at the National Institute of Infectious Diseases in Japan with primer-probe sets previously described [4]; thus, we diagnosed the patient with Zika fever. His fever and other symptoms subsided a day after first presentation and his rash disappeared over the next few days.

Case 2

A previously healthy Japanese woman in her early 30s presented to our hospital in the beginning of January 2014 for retro-orbital pain, slight fever (self-reported), rash, and itches. Her retro-orbital pain and mild fever had appeared five days prior to her visit at our hospital, while the rash and itches appeared on the day before the visit. She had travelled to Bora Bora where she stayed for 10 days starting mid-December 2013 for sightseeing with a companion. The first symptoms occurred six days after this journey. She had used insect repellent during her travels, but reported mosquito bites. She was afebrile and in good general condition at the first presentation to the hospital. On examination, both bulbar conjunctivas appeared

FIGURE 1

Conjunctivitis in a case of imported Zika virus infection from French Polynesia, Japan, January 2014



Although the patient was afebrile upon examination, both bulbar conjunctivas appeared congested.

FIGURE 2

Maculopapular rash on the back in a case of imported Zika virus infection from French Polynesia, Japan, January 2014



congested (Figure 1). She had maculopapular rash on her face, trunk, and extremities (Figure 2).

Laboratory tests on the day of first presentation at the hospital revealed leucopenia ($3,500 \times 10^6/L$; norm: $3,500-8,500 \times 10^6/L$) and thrombocytopenia ($14,400 \times 10^6/L$; norm: $15,000-35,000 \times 10^6/L$). Real-time RT-PCR assays, performed at the National Institute of Infectious Diseases, gave negative results for ZIKV RNA in serum but presence of the virus was detected in urine. The patient was diagnosed with Zika fever. Her leucocyte and platelet levels returned to the normal range 12 days after first presentation at the hospital. The positive versus negative ratios (P/N ratio) of Zika-specific IgM antibodies were positive in two serum samples collected on the first day at the hospital and five days later (P/N ratios = 2.4 and 9.8, respectively; ratios were considered positive when greater than or equal to 2.0). The neutralising antibody titres of the serum in these two consecutive samples were $PRNT_{50}=1:20$ and $PRNT_{50}=1:1,280$, respectively.

Background

Zika fever is a febrile or subfebrile illness caused by ZIKV, which mainly spreads through the bite of infected mosquitoes. ZIKV is a member of the family Flaviviridae, which includes dengue viruses, West Nile, and yellow fever viruses [5]. The most common symptoms reported in confirmed ZIKV infections are fever, headache, malaise, maculopapular rash, fatigue or myalgia, and arthritis and arthralgia [6].

ZIKV was first isolated from the blood of a sentinel rhesus monkey from the Zika Forest in Uganda [7]. Serological studies and isolation of ZIKV strains have

subsequently demonstrated that the virus has a wide geographical distribution, including eastern and western Africa, south and south-east Asia, and Micronesia [8], where in 2007, an outbreak of Zika fever was reported on Yap Island [9].

Phylogenetic analysis of the Zika virus sequence retrieved from case 2

Phylogenetic analysis of the partial ZIKV E-protein genome sequence (470 bp, GenBank accession number: AB908162*) obtained from the urine sample of case 2, shows that this sequence has 99.1% identity with the sequence of a ZIKV strain isolated from Cambodia in 2010 (GenBank accession number: JN860885), and 97.9% identity with the sequence of a ZIKV strain isolated in Yap islands in 2007 (GenBank accession number: EU545988) (Figure 3). The sequence from case 2 sample was also similar to previously identified ZIKV sequences of strains in Asia and Micronesia [8]. In the phylogenetic tree, these sequences formed a distinct cluster from that of sequences from Zika viruses of African origin. Further studies using full-length genome of the ZIKV will address the similarity between virus strains of the African and Asian clusters.

Discussion and conclusion

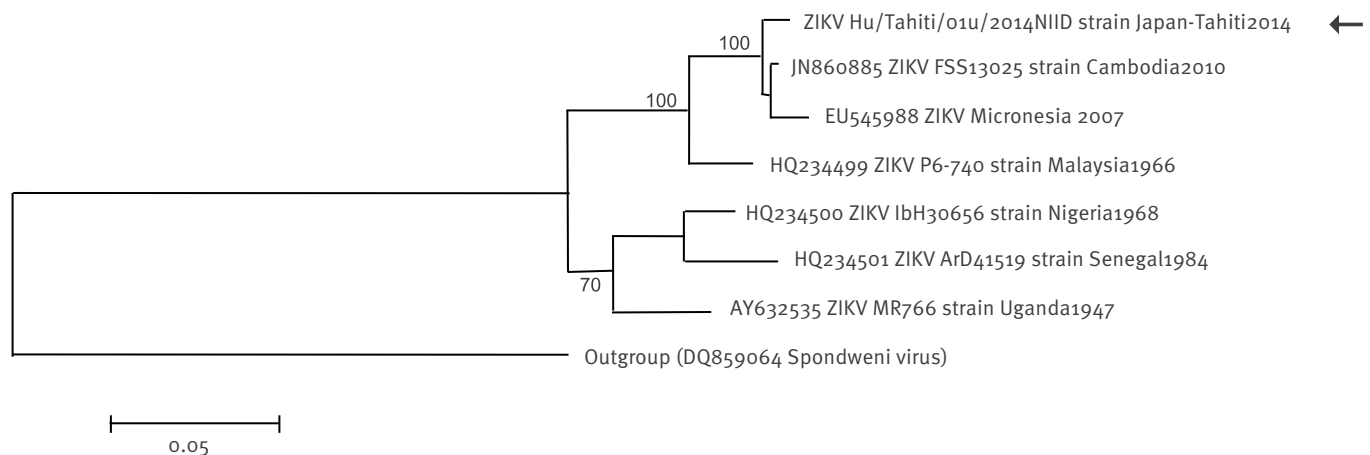
Our two cases are among the first imported cases found linked to the recent outbreak in French Polynesia starting in 2013. They occur shortly after 26 imported cases into New Caledonia from the same outbreak, as well as the report of one indigenous case [10]. Aside from cases related to French Polynesia, imported Zika fever cases have been previously identified in travellers returning from Africa and south-east Asia. These include a case of sexually transmitted Zika fever following two imported cases from Senegal into the United States, and an imported case of Zika fever from Indonesia to Australia [11,12]. Two imported cases from Thailand, one to Canada [13] and one to Germany [14] have also recently been reported.

Although the numbers of imported cases described so far are limited, the possibilities of ZIKV infections to be underdiagnosed and underreported are high due to generally mild symptoms and self-limited disease. Additionally, due to the similarity of ZIKV disease symptoms to those of dengue and chikungunya, differential diagnosis is required to define the extent of ZIKV epidemic. Importantly, as dengue virus (DENV) outbreaks also occur in French Polynesia [2], differential diagnosis between ZIKV infection and dengue is required in cases related to this area. Because of the ongoing dengue epidemic in Bora Bora, DENV infection was excluded in both cases in this study, by confirming that the serum samples were negative for both dengue virus nonstructural glycoprotein-1 (NS1) antigen and IgM/IgG antibodies, using rapid diagnostic kits (SD Bioline Dengue Duo Combo, Alere Medical, Inc.).

In this study, the two cases of ZIKV infection had not only leucopenia but also mild thrombocytopenia.

FIGURE 3

Phylogenetic analysis of a Zika virus sequence derived from a case of imported Zika virus infection from French Polynesia, Japan, January 2014



The phylogenetic tree was based on partial E-protein nucleotide sequences and compiled using the neighbour joining method (Genetyx, Japan). The sequence of the Spondweni virus (GenBank accession number DQ859064) was used as an outgroup. Bootstrap percentages based on 1,000 replicates are shown on the tree nodes. The sequence of the case of imported Zika virus infection from French Polynesia to Japan in January 2014 is indicated with an arrow. Scale bar (0.05) indicates nucleotide substitutions per site.

Previous investigators reported leucopenia, but not thrombocytopenia in patients with ZIKV infection [12]. Our two cases suggest that ZIKV infection can be associated with clinical features including thrombocytopenia and leucopenia, and shares similar clinical features to those of dengue fever and yellow fever.

In the second case identified in this study, viral RNA was negative in the serum sample but was positive in the urine sample. To our knowledge, this is the first case diagnosed by detection of Zika viral particles in urine. Detection of DENV genome in urine after disappearance of the viral genome in serum samples by real-time RT-PCR has been a useful laboratory diagnostic method [15]. Our case suggests that detection of Zika virus genome in urine by real-time RT-PCR is useful to confirm ZIKV infection, particularly after disappearance of viraemia in serum.

Phylogenetic analysis revealed that the ZIKV genome sequences of case 2, had a high sequence homology with recent strains from Asia and Micronesia, including those detected in Cambodia in 2010, but sequence homology was low with a strain isolated in 1947, the Ugandan prototype MR766 strain [4].

The ongoing ZIKV outbreaks in French Polynesia and the confirmation of ZIKV viraemic travellers in our study suggests that in addition to enhanced and continued surveillance efforts, awareness among health-care professionals should be raised that ZIKV infection ought to be considered as differential diagnosis in febrile patients with rash returning from areas affected by this virus. Further prevention measures, such as offering advice on the use of insect repellents during

travel to regions with outbreaks, would be important for ZIKV disease control.

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Conflict of interest

None declared.

Authors' contributions

Satoshi Kutsuna collected the data and drafted the manuscript; Yasuyuki Kato participated in the coordination and concept of the manuscript and edited the manuscript and helped with the draft of the manuscript; Tomohiko Takasaki, Meng Ling Moi, Akira Kotaki performed real-time RT-PCR and performed the phylogenetic analysis; Haruka Uemura, Takashi Matono, Yoshihiro Fujiya, Momoko Mawatari, Nozomi Takeshita, Kayoko Hayakawa collected the data and participated in the concept of the manuscript; Shuzo Kanagawa, Norio Ohmagari revised the article for intellectual content. All authors read and critically revised the first as well as the subsequent and final drafts of this manuscript.

* Addendum:

The GenBank accession number of the partial Zika virus nucleotide sequence derived from a sample obtained from case 2 was added on 07 February 2014.

* Erratum:

The title of this manuscript was initially wrong at the time of publication: 'Two cases of Zika fever imported from French Polynesia to Japan, December to January 2013'. The mistake was corrected on 31 January 2014.

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First case of laboratory-confirmed Zika virus infection imported into Europe, November 2013

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In November 2013, an acute Zika virus (ZIKV) infection was diagnosed in a German traveller returning from Thailand. The patient reported a clinical picture resembling dengue fever. Serological investigations revealed anti-ZIKV-IgM and -IgG, as well as ZIKV-specific neutralising antibodies in the patient's blood. In Europe, viraemic travellers may become a source of local transmission of ZIKV, because *Aedes albopictus* (Skuse) and *Ae. aegypti* (Linnaeus) are invasive mosquitoes and competent vectors for ZIKV.

We report the clinical and laboratory findings of a Zika virus (ZIKV) infection imported into Europe by a German traveller from Thailand, in winter of 2013.

Case description

A previously healthy German traveller in his early 50s was seen at a tertiary hospital, Germany, on 22 November 2013, after returning from a vacation in Thailand. During the patient's three-week round trip (in early November) which included visits to Phuket, Krabi, Ko Jum, and Ko Lanta, he developed joint pain and swelling of his left ankle and foot on 12 days after entering the country. Pain and swelling was followed by a maculopapular rash on his back and chest that later spread to the face, arms, and legs over a period of four days before fading. Concomitantly, the patient suffered from malaise, fever (self-reported), and chills. Fever and shivering were treated by self-medication with non-steroidal anti-inflammatory drugs and only lasted for one day. The patient had noted several mosquito bites previously, despite using insect repellents regularly. He had sought pre-travel advice and his travel partner did not have any symptoms and also did not develop any.

Upon return to Germany, the patient was asymptomatic except for the subjective complaint of ongoing exhaustion. Physical examination was normal and no particular treatment was initiated. Laboratory parameters 10 days after disease onset revealed a slightly increased

C-reactive protein level (5.9 mg/L; normal value <5.0), a normal leucocyte count of 8,200 g/μL (45% lymphocytes, 5% monocytes, and a mildly decreased relative neutrophil count of 47% (normal range: 50–75%)). Platelet count was normal with 238,000 g/μL. Lactate dehydrogenase levels were elevated (311 U/L; normal <262 U/L), with an increased plasma fibrinogen concentration (422 mg/dL; normal range: 180–400 mg/dL) and serum ferritin concentration (486 ng/mL; normal range: 30–400). Serum electrophoresis, clotting tests, kidney and liver function tests were normal except for an increased gamma-glutamyltransferase activity of 81 U/L (normal <60 U/L).

A serum sample from the same day (10 days after symptom onset) showed a positive result for anti-dengue virus (DENV)-IgM in both the indirect immunofluorescence assay (IIFA), according to [1-3] and rapid test (SD BIOLINE Dengue Duo NS1 Ag + Ab Combo). However, anti-DENV-IgG was not detected in either test. Testing for DENV nonstructural protein-1 (NS1) antigen (tested by enzyme-linked immunosorbent assay (ELISA): Bio-Rad Platelia Dengue NS1 Ag) and rapid test (SD BIOLINE Dengue Duo NS1 Ag + Ab Combo) were also negative. The detection of isolated anti-DENV-IgM prompted us to investigate a probable flavivirus etiology other than DENV of the patient's illness. Serological tests for Japanese encephalitis virus (JEV), West Nile virus (WNV), yellow fever virus (YFV), tick-borne encephalitis virus (TBEV), and ZIKV were performed according to [1-3] and the IIFAs showed only positive results for anti-ZIKV-IgM and -IgG antibodies (Table), demonstrating an acute or recent ZIKV-infection of the patient. Serological tests for chikungunya virus (CHIKV) were negative (Table).

ZIKV-specific real-time reverse transcription-polymerase chain reaction (RT-PCR) (in-house) with primers ZIKAf (5'-TGGAGATGAGTACATGTATG-3'), ZIKAr (5'-GGTAGATGTTGTCAAGAAG-3'), probe – labeled with 6-carboxyfluorescein (FAM) and black hole quencher 1

TABLE

Serological results of a case of Zika virus infection from Thailand imported into Germany, November 2013

Antibody or antigen tested	Serum samples taken after symptom onset (days)		
	10	31	67
Anti-ZIKV-IgG ^a	1:5,120	1:2,560	1:2,560
Anti-ZIKV-IgM ^a	1:10,240	1:2,560	1:320
Anti-DENV-IgG ^a	<1:20	1:80	1:160
Anti-DENV-IgM ^a	1:40	<1:20	<1:20
DENV NS1 ^b	Negative (0.1 arbitrary units)	Negative (0.2 arbitrary units)	Negative (0.1 arbitrary units)
Anti-JEV-IgG ^a	<1:20	1:40	1:20
Anti-JEV-IgM ^a	<1:20	<1:20	<1:20
Anti-WNV-IgG ^a	<1:20	1:20	1:80
Anti-WNV-IgM ^a	<1:20	<1:20	<1:20
Anti-YFV-IgG ^a	<1:20	<1:20	1:20
Anti-YFV-IgM ^a	<1:20	<1:20	<1:20
Anti-CHIKV-IgG ^a	<1:20	<1:20	<1:20
Anti-CHIKV-IgM ^a	<1:20	<1:20	<1:20

CHIKV: chikungunya virus; DENV: dengue virus; JEV: Japanese encephalitis virus; NS1: nonstructural protein-1; WNV: West Nile virus; YFV: yellow fever virus; ZIKV: Zika virus.

^a Indirect immunofluorescence assay (IIFA) titres <1:20 for serum were considered negative [1-3].

^b SD BIOLINE Dengue Duo NS1 Ag + Ab Combo and Bio-Rad Platelia Dengue NS1 Ag.

(BHQ-1) – ZIKAp (5'-FAM-CTGATGAAGGCCATGCACACTG-BHQ1-3') was negative on serum. Generic flavivirus real-time RT-PCR [4] was negative as well on serum. A significant 5-fold anti-ZIKV-IgM titre decrease in the IIFA was demonstrated in the third serum sample collected 67 days after disease onset (Table). The presence of ZIKV-specific neutralising antibodies in the third serum sample was confirmed by a virus neutralisation assay. No laboratory investigation was conducted with the travel partner.

Background

ZIKV is a mosquito-borne RNA virus of the *Flaviviridae* family causing a dengue fever-like syndrome in humans. The virus was first isolated in 1947 from a febrile sentinel rhesus monkey in the Zika Forest of Uganda [5]. ZIKV virus is thought to be maintained in a sylvatic cycle involving non-human primates and several *Aedes* species (*Ae. africanus*, *Ae. aegypti*, and others) as mosquito vectors [6-8]. Human infection is acquired after an infective mosquito bite in endemic countries. However, the possibility of a secondary sexual transmission has been reported recently [9]. The virus is endemic in Africa and south-east Asia [8], and phylogenetic analysis suggested that African and Asian strains emerged as two distinct lineages [10-11]. ZIKV has caused an outbreak involving 49 confirmed and 59 probable cases on Yap Island, Federated States of Micronesia, in 2007 [12]. This outbreak highlighted the potential of the virus as an emerging pathogen [9], and epidemiological and phylogenetic studies provided

evidence that the outbreak strain has been introduced from south-east Asia [10].

The most common signs and symptoms of ZIKV infection are rash, fever, arthralgia, myalgia, headache, and conjunctivitis. The rash is most often maculopapular. Occasionally, oedema, sore throat, cough, vomiting, and loose bowels are reported [11-13]. ZIKV infection can easily be confused with dengue and might be misdiagnosed during local dengue outbreaks [8]. ZIKV-associated illness may thus be underreported or misdiagnosed [9].

In contrast to acute dengue cases, our patient neither showed elevated aspartate amino transferase (AST) or alanine amino transferase (ALT) levels, nor thrombocytopenia. It is unclear whether these test results may help in differentiating ZIKV from dengue cases, as information about laboratory data during ZIKV infection is very scarce. An Australian case [11] did not show thrombocytopenia or elevated liver function tests either. It was reported recently that a low platelet count is a key variable distinguishing between dengue versus chikungunya [14], the latter being another mosquito-borne virus infection with similar clinical presentation and geographical distribution. Chikungunya is thus also an important differential diagnosis for ZIKV disease and future studies might address this issue for ZIKV.

Despite the virus endemicity in many geographical areas and its potential to cause outbreaks, imported cases to non-endemic areas are rarely reported. In 2013, one imported case from Indonesia to Australia and one imported case from Thailand to Canada were diagnosed in travellers [11,15]. Also in the Australian and Canadian cases, anti-DENV-IgM was positive and DENV NS1 antigen testing was negative. In both cases, ZIKV infection was diagnosed after sequencing of a positive generic flavivirus RT-PCR amplicon. Four further cases of imported ZIKV to temperate regions have been reported in American scientists who had returned from Senegal and in Japanese travellers who returned from French Polynesia, where a ZIKV outbreak is currently ongoing [16,17]. A secondary infection in the wife of one of the American patients was assumed to be due to sexual contact [9]. The ZIKV outbreak in French Polynesia so far comprises more than 361 laboratory-confirmed cases [18]. The first indigenous infection in New Caledonia was recently reported suggesting the spread of ZIKV, as 26 imported cases of ZIKV infection from French Polynesia have been observed in this territory [19].

Conclusions

This report constitutes, to the best of our knowledge, the first laboratory-confirmed case of a ZIKV infection imported into Europe. The case highlights that unusual DENV serology results might be caused by a flavivirus different than DENV despite a similar clinical picture. A serological study after the Yap outbreak indicated that ZIKV-infected patients can be positive in anti-DENV-IgM assays [20], as also experienced in our case. This cross-reaction in the Yap outbreak was seen especially if ZIKV was a secondary flavivirus infection. These findings underscore the importance of a careful diagnostic investigation in travellers suspected with dengue, and the well-known serological cross-reactions in the flavivirus group. Thus, the rate at which seemingly imported dengue cases among travellers from endemic areas in the recent years were actually ZIKV infections remains a question.

In all published cases of imported ZIKV infections, in outbreak and sporadic endemic cases, the symptoms were dengue-like. Clinicians, virologists, and public health authorities should thus be aware of this emerging flavivirus infection. As the local transmission of DENV by previously introduced competent vectors in non-endemic countries has recently been reported from Croatia, France and Madeira [2,21,22], there might be the risk of a similar establishment in Europe of ZIKV, after import by viraemic travellers, in particular in areas where ZIKV competent vectors *Ae. albopictus* and *Ae. aegypti* are present.

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Conflict of interest

None declared.

Authors' contributions

Wrote the manuscript: JSC, SG, DT, JR, SS, GH; performed laboratory or epidemiological investigations: JSC, PE, MG, JR, GH, DT; performed data analysis: JSC, PE, JR, GH.

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Zika virus infection complicated by Guillain-Barré syndrome – case report, French Polynesia, December 2013

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Zika fever, considered as an emerging disease of arboviral origin, because of its expanding geographic area, is known as a benign infection usually presenting as an influenza-like illness with cutaneous rash. So far, Zika virus infection has never led to hospitalisation. We describe the first case of Guillain-Barré syndrome (GBS) occurring immediately after a Zika virus infection, during the current Zika and type 1 and 3 dengue fever co-epidemics in French Polynesia.

We report on a French Polynesian patient presenting a Zika virus (ZIKA) infection complicated by Guillain-Barré syndrome (GBS).

Clinical description

In November 2013, a Polynesian woman in her early 40s, with no past medical history with the exception of acute articular rheumatism, was hospitalised in our institution for neurological deficits. She had been evaluated one day before (Day 0: onset of neurological disorders) at the emergency department for paraesthesia of the four limb extremities and discharged. At Day 1, she was admitted to the department of neurology through the emergency department because paraesthesia had evolved into ascendant muscular weakness suggestive of GBS. At Day 3, she developed a tetraparesis predominant in the lower limbs, with paraesthesia of the extremities, diffuse myalgia, and a bilateral but asymmetric peripheral facial palsy. Deep tendon reflexes were abolished. There was no respiratory nor deglutition disorders. The patient developed chest pain related to a sustained ventricular tachycardia, and orthostatic hypotension, both suggestive of dysautonomia. The echocardiography was normal, without signs of pericarditis or myocarditis. The electromyogram confirmed a diffuse demyelinating disorder, with

elevated distal motor latency, elongated F-wave, conduction block and acute denervation, without axonal abnormalities. The administration of intravenous polyvalent immunoglobulin (0.4 g/kg/day for 5 days) allowed a favourable evolution, with no respiratory impairment necessitating tracheotomy or intensive care unit monitoring, and the patient was discharged home at Day 13. Paraparesis persisted after the end of hospitalisation, that imposed the use of a walking frame, and the facial palsy slowly disappeared. At Day 40, she was able to walk without help and had a satisfying muscular strength score of 85/100.

Retrospectively, anamnestic data revealed that she had suffered from an influenza-like syndrome at Day – 7, with myalgia, febricula, cutaneous rash, and conjunctivitis. Because an epidemic of Zika fever, which is still ongoing [1], had begun a few weeks prior to the patient presenting this syndrome, Zika fever was suspected.

Laboratory analysis

Laboratory findings showed no inflammatory syndrome and the blood count was normal. A twofold increase in transaminase level was observed. The analysis of cerebrospinal fluid (CSF) disclosed an albuminocytological dissociation with 1.66 g/L proteins (norm: 0.28–0.52) and 7 white cells/mL (norm<10). Glycorrhachia was normal at 0.60 g/L. Usual aetiologies of GBS were eliminated: serological tests for human immunodeficiency virus (HIV), hepatitis B and C, *Campylobacter jejuni* and *Leptospira* were negative; and serological tests for cytomegalovirus, Epstein-Barr virus, and herpes simplex virus type 1 and 2 concluded to resolute infections.

Direct detection of dengue virus (DENV) by non-structural protein 1 (NS1) antigen (SD Bioline Dengue NS1 Ag

ELISA, ALERE Australia) and reverse transcription-polymerase chain reaction (RT-PCR) [2], and ZIKA by RT-PCR [3], were negative on blood samples eight days after the beginning of influenza-like symptoms (corresponding to Day 1), prior to the administration of intravenous immunoglobulin. Blood samples taken at eight and 28 days after the beginning of the influenza-like syndrome were both positive for ZIKA-specific IgM and ZIKA- and DENV-specific IgG, assessed by in-house enzyme-linked immunosorbent assays (in-house IgM antibody capture (MAC)- enzyme-linked immunosorbent assay (ELISA) and indirect IgG ELISA using inactivated antigen). On the last serum specimen sampled 28 days after the onset of influenza like syndrome, antibody specificity was determined by plaque reduction neutralisation test (PRNT) against serotype 1 to 4 DENV (DENV1–4) and ZIKA. A 90% neutralisation titre $\geq 1/320$ for DENV1, 1/80 for DENV2, $\geq 1/320$ for DENV3, 1/20 for DENV4 and $\geq 1/320$ for ZIKA confirmed that neutralising antibodies against ZIKA and the four DENV serotypes were present in the sera of the patient. These serological analyses indicated a recent infection by ZIKA, and argued for resolute infections by DENV1–4.

Background on Zika virus infections

Discovered in 1947 in the Zika forest in Uganda, ZIKA is an arbovirus of the flavivirus genus belonging to the *flaviviridae* family, as dengue, yellow fever, Japanese encephalitis, West Nile, and Saint-Louis encephalitis viruses. First human cases of ZIKA infection were described in the 1960s, first in Africa, then in south-east Asia [4–6]. Until 2007 when a large epidemic was described in Yap (Micronesia) [7], ZIKA infections remained limited to sporadic cases or small-scale epidemics. During the epidemic in Yap, three quarters of the local population are estimated to have been infected [7]. The expanding distribution area of ZIKA makes Zika fever an emerging disease [8], confirmed by the present epidemic affecting French Polynesia since October 2013, and the New Caledonian reported cases since the end of 2013 [1].

The real incidence of Zika fever is unknown, due to clinical manifestations mimicking dengue virus infection, and to lack of simple reliable laboratory diagnostic tests. In endemic areas, epidemiological studies showed a high prevalence of antibodies against ZIKA [9,10]. For instance, Yap's epidemic in 2007 resulted in an attack rate of 14.6/1,000 inhabitants and a seroprevalence of 75% after the epidemic. However, this prevalence is certainly overestimated, due to cross-reaction between antibodies directed against ZIKA and other arboviruses such as DENV [3,11].

Like other arboviral diseases, ZIKA is transmitted by arthropods, mainly involving vectors of the *Aedes* genus, as ZIKA was isolated from numerous species of *Aedes* mosquitoes in different parts of the world [12–14]. Interestingly, since the first description of *Ae. albopictus* as a potential vector of ZIKA in 2007 by Wong et al., other reports have suggested that the rapid

worldwide expansion of this vector could be responsible for the emergence of new ZIKA infection epidemics, including in urban areas [15,16]. Based on epidemiological evidence, *Ae. aegypti* and *Ae. polynesiensis* are suspected to be the vectors for the ongoing French Polynesia's epidemic (data not shown). The abundance of competent vectors in the Pacific areas and air travel of viraemic individuals between Pacific island countries and territories are very likely to account for the expansion of ZIKA in this part of the world.

Infection is reported to be symptomatic in 18% of cases only [7]. When symptomatic, ZIKA infection usually presents as an influenza-like syndrome, often mistaken with other arboviral infections like dengue or chikungunya. The typical form of the disease associates a low-grade fever (between 37.8°C and 38.5°C), arthralgia, notably of small joints of hands and feet, with possible swollen joints, myalgia, headache, retroocular headaches, conjunctivitis, and cutaneous maculopapular rash. Digestive troubles (abdominal pain, diarrhoea, constipation), mucous membrane ulcerations (aphthae), and pruritus can be more rarely observed. A post-infection asthenia seems to be frequent [5,7,17].

Confirmed diagnosis is given by RT-PCR, which specifically detects the virus during viraemia [3]. In-house ELISA serological tests can testify the presence of ZIKA IgM and flaviviruses IgG, whereby specificity is determined by seroneutralisation.

Discussion and conclusion

During this ongoing Zika fever outbreak in French Polynesia, we report the first case of GBS developing seven days after an influenza-like illness evoking ZIKA infection. Based on IgM/IgG serological results and PNRT which, according to our experience, is reliable and specific enough to differentiate a recent ZIKA infection from cross-reactions due to former infections to DENV, we believe that this is the first case of hospitalisation because of a severe ZIKA infection.

Since the beginning of this epidemic, and as up to 8,200 cases of ZIKA infection have already been reported of a 268,000 total population, the incidence of GBS has been multiplied by 20 in French Polynesia (data not shown), raising the assumption of a potential implication of ZIKA.

Underlying physiopathological mechanisms of Zika-related GBS is unknown, and could be of immunological origin as described with other infectious agents [18]. There is also no explanation for the emergence of this previously undescribed complication, which could lie in a genetic evolution of the virus to a more pathogenic genotype, or a particular susceptibility in the Polynesian population.

As suggested by DENV and ZIKA serological tests in our patient, the simultaneous epidemics of type 1 and 3 dengue fever may also be a predisposing factor

for developing GBS during Zika fever, as DENV infection had also been associated with GBS [19,20]. Our patient, like part of others who also presented a GBS, harboured serological markers of resolute dengue and recent ZIKA infections. This raises the hypothesis of a sequential arboviral immune stimulation responsible for such unusual clustering of GBS cases during concurrent circulation of ZIKA and two dengue serotypes. The risk of developing GBS would be consequently underlain by a specific sequence of DENV and ZIKA infections.

Therefore in endemic areas, clinician should be aware of the risk of diffuse demyelinating disorder in case of ZIKA infection.

Conflict of interest

None declared.

Authors' contributions

EO, LW, FV wrote the manuscript. EO, LW, PL, FG took part in the clinical management of the patient. SL, DM collaborated in molecular biology techniques. ILG collaborated on the virological investigation and on the manuscript writing. All authors participated in the outbreak investigation. All authors read and approved the final manuscript.

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Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014

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A Zika virus (ZIKAV) outbreak started in October 2013 in French Polynesia, South Pacific. We describe here the clinical and laboratory features of two mothers and their newborns who had ZIKAV infection as confirmed by ZIKAV RT-PCR performed on serum collected within four days post-delivery in date. The infants' infection most probably occurred by transplacental transmission or during delivery. Attention should be paid to ZIKAV-infected pregnant women and their newborns, as data on the impact on them are limited.

Since October 2013, French Polynesia has experienced the largest outbreak of Zika virus (ZIKAV) infection ever reported, with an estimate of 28,000 ZIKAV infections in early February 2014 (about 11% of the population) [1,2]. We report here evidence of perinatal transmission of ZIKAV in French Polynesia in December 2013 and February 2014.

Clinical and laboratory description

Case 1

In December 2013, a woman in her early 30s (Mother 1), who presented at hospital at 38 weeks' gestation, vaginally delivered a healthy newborn (Apgar score 10/10) (Newborn 1), who was immediately breastfed. The mother had a mild pruritic rash without fever that had started two days before delivery and lasted up to two days post-delivery (day 2). Clinical examination of the infant remained unremarkable from birth to five days after delivery, when the infant was discharged. The infant evolved favourably and the mother recovered favourably.

Case 2

In February 2014, a woman in her early 40s (Mother 2), who had been monitored for gestational diabetes and intrauterine growth restriction diagnosed during the second trimester of pregnancy, presented at hospital at 38 weeks' gestation for delivery. She underwent a caesarean section due to pregnancy complications. Her newborn (Newborn 2) had severe hypotrophy and Apgar score 8/9/9. Enteral nutrition with formula milk

for premature newborns was started due to hypoglycaemia and breastfeeding was started, in addition, from the third day post-delivery (day 3). On day 3, the mother presented a mild fever (37.5–38 °C) with pruritic rash and myalgia. The following day, after a three-hour ultraviolet light session for neonatal jaundice, the newborn presented transiently an isolated diffuse rash. Both mother and infant evolved favourably.

Laboratory features

All available samples collected from Mother 1 and Newborn 1 until day 3 and from Mother 2 and Newborn 2 until day 13 were tested for ZIKAV and dengue virus (DENV). No other pathogens were tested for, given the co-circulation of DENV (serotypes 1 and 3) [3] and ZIKAV.

The test for ZIKAV was real-time reverse-transcription (RT) PCR using two primers/probe amplification sets specific for ZIKAV [4]: results were reported positive when the two amplifications occurred (threshold cycle less than 38.5). A standard curve using serial dilutions of known concentrations of a ZIKAV RNA synthetic transcript was included within the RT-PCR run to estimate the RNA loads. Both mothers and both newborns had ZIKAV infection confirmed by positive RT-PCR result on at least one serum sample.

Breast milk samples from both mothers were inoculated on Vero cells in order to detect replicative ZIKAV and were also tested by RT-PCR. The samples gave positive RT-PCR results, but no replicative ZIKAV particles were detected in cell culture. Blood cell counts were in the normal range, except for Newborn 2, who displayed a low platelet count from day 3 ($65 \times 10^9/\text{mL}$) to day 7 ($106 \times 10^9/\text{mL}$) (norm: $>150 \times 10^9/\text{mL}$) and an elevated level of total bilirubin on day 3 ($247 \mu\text{mol/L}$) (norm: $<200 \mu\text{mol/L}$); total protein and C-reactive protein levels were within the normal range.

All samples tested by ZIKAV RT-PCR were also tested for DENV using a multiplex RT-PCR [5]: all were negative.

TABLE

Biological features of mothers and newborns with evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014

Number of days from delivery	Clinical picture				Zika virus RT-PCR and culture			
	Mother 1	Newborn 1	Mother 2	Newborn 2	Mother 1	Newborn 1	Mother 2	Newborn 2
-2	Rash	-	-	-	-	-	-	-
0	Delivery	Breastfeeding	Delivery	Enteral nutrition	-	-	-	Serum RT-PCR: Neg
1	Rash	-	-	-	-	-	Serum RT-PCR: Pos (59×10^4 copies/mL)	-
2	Rash	-	-	-	Serum RT-PCR: Pos (7.0×10^4 copies/mL) Saliva RT-PCR: Pos ^a	-	-	-
3	-	-	Rash, mild fever (37.5–38°C)	Breastfeeding	Breast milk RT-PCR: Pos (205×10^4 copies/mL) Breast milk culture: Neg	Serum RT-PCR: Pos (65×10^4 copies/mL) Saliva RT-PCR: Pos ^a	-	Serum RT-PCR: Neg
4	-	-	-	Rash	-	-	-	Serum RT-PCR: Pos (62×10^4 copies/mL)
5	-	-	-	-	-	Serum RT-PCR: Pos (2.6×10^6 copies/mL)	-	-
7	-	-	-	-	-	-	-	Serum RT-PCR: Pos (69×10^4 copies/mL)
8	-	-	-	-	-	Serum RT-PCR: Neg Breast milk RT-PCR: Pos (2.9×10^4 copies/mL) Urine RT-PCR: Pos (16×10^4 copies/mL) Breast milk culture: Neg	-	Urine RT-PCR: Pos (20×10^4 copies/mL)
11	-	-	-	-	-	-	Serum RT-PCR: Neg	Urine RT-PCR: Neg
13	-	-	-	-	-	-	Serum RT-PCR: Neg	-

Neg.: negative; Pos.: positive; RT: real-time reverse-transcription.

^a Viral load was not determined on saliva samples.

Detailed laboratory results for ZIKAV PCR and culture are reported in the Table.

Ethics approval

Informed written consent was obtained from the two mothers and publication of data related to ZIKAV infections was approved by the Ethics Committee of French Polynesia (reference 66/CEPF).

Background

ZIKAV, first isolated in 1947 from a rhesus monkey in Zika Forest, Uganda, is an arthropod-borne virus (arbovirus) belonging to the *Flaviviridae* family and the *Flavivirus* genus [6]. Since the 1960s, human cases have been sporadically reported in Asia and Africa [7], but the first large documented outbreak occurred in 2007 in Yap Island, Micronesia, in the North Pacific, where physicians reported an outbreak characterised by rash, conjunctivitis and arthralgia [8].

ZIKAV is transmitted by mosquitoes, especially *Aedes* species [7]. Direct inter-human transmission, most likely by sexual intercourse, has been described [9]. As little is known about ZIKAV transmission, we investigated other possible modes of transmission. The cases studied provide the first reported evidence of perinatal transmission of ZIKAV.

Discussion

Perinatal transmission of arbovirus has been reported for DENV [10-14], chikungunya virus (CHIKV) [15,16], West Nile virus (WNV) [17,18] and yellow fever virus (YFV) [19,20]. Breast milk transmission has been reported for DENV [14] and WNV [18] and has been suspected for the vaccine strain of YFV [20]. Severe consequences of arbovirus materno-fetal transmission have been reported, notably for CHIKV (encephalopathy and haemorrhagic fever) [16] and DENV (preterm delivery, fetal death, low birth weight, fetal anomalies, prematurity and acute fetal distress during labour) [10,12].

The possible routes of perinatal transmission are transplacental, during delivery, during breastfeeding and by close contact between the mother and her newborn. The sera from the mothers were RT-PCR positive within two days post-delivery and those of their newborns within four days post-delivery. The observation that Mother 1 had displayed a rash two days before delivery and was confirmed ZIKAV RT-PCR positive on two days post-delivery suggests that she was viraemic before and during delivery. Mother 2's serum was RT-PCR positive the day after delivery, suggesting that she was viraemic or at least incubating ZIKAV at the time of delivery. As there are no firm data on the delay necessary for ZIKAV to become detectable by RT-PCR in serum after exposure, the observation that ZIKAV RNA was detectable as early as three and four days post-delivery in the newborns does not provide evidence of transplacental transmission rather than contamination during delivery. Evidence of transplacental transmission would have been the delivery of a viraemic

newborn, but the serum sample collected the day of delivery from Newborn 2 was RT-PCR negative; no sample was available on the delivery day for Newborn 1.

In November 2013, a first case of perinatal transfusion of ZIKAV was suspected in French Polynesia: the newborn displayed a maculopapular rash at delivery and the mother reported a ZIKAV infection-like syndrome two weeks before (data not shown). Unfortunately, however, virological investigations were not performed.

The detection of ZIKAV RNA by PCR in breast milk samples in our study raises the question of possible transmission by breastfeeding. The fact that replicative ZIKAV was not found in breast milk samples makes contamination by this route unlikely. The finding that RT-PCR on Newborn 2's serum was positive the day following the start of breast feeding can reasonably exclude this route of contamination for this infant. The ZIKV RNA load reported in the two breast milk samples (2.9×10^4 and 205×10^4 copies /mL) were higher than the DENV RNA load reported in a suspected case of DENV breast milk transmission ($>0.01 \times 10^4$ and $>0.1 \times 10^4$ copies /mL) in New Caledonia in 2012 [14]. Of interest, CHIKV RNA was not detected from 20 milk samples collected from breastfeeding viraemic mothers during an outbreak of CHIKV infection in Réunion Island in 2005-06 [16].

As saliva samples from Mother 1 and Newborn 1 gave positive RT-PCR results, contamination by close contact cannot be excluded. However, it is currently unknown whether saliva actually contains replicative ZIKV.

Contamination of the newborns as a result of being bitten by an infected mosquito bite seems fairly improbable because of the air-conditioned rooms in the hospital.

Even though the newborns had similar ZIKAV RNA loads (about 60×10^4 copies/mL) in serum, Newborn 1 remained asymptomatic, whereas Newborn 2 displayed a maculopapular rash and thrombocytopenia. This newborn also had low birth weight but we do not have data to suggest this was due to ZIKAV infection, especially as there was intrauterine growth restriction from the second trimester of pregnancy and gestational diabetes.

During this large outbreak, many pregnant women could have been infected by ZIKAV, but we did not register any increase in the number of fetal deaths or premature births.

Conclusions

Given the severe neonatal diseases reported with other arbovirus infections, such as chikungunya [16] and dengue [10,12], we recommend close monitoring of perinatal ZIKAV infections. Due to the high ZIKAV RNA load detected in breast milk, and even though no replicative

ZIKAV particles were detected, ZIKAV transmission by breastfeeding must be considered.

Zika fever has been reported in tourists returning from French Polynesia to Japan in 2013–14 [21]. An outbreak of ZIKAV infection was also declared in February 2014 in New Caledonia, in the South Pacific [22]. Patients living in or returning from ZIKAV-endemic or epidemic areas presenting with a ‘dengue-like’ syndrome but testing negative for DENV should be tested for ZIKAV, with attention paid to infected pregnant women and their newborns, as data on the impact of the infection on them are limited.

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Conflict of interest

None declared.

Author’s contributions

MB, SL, VM CL and DM wrote the manuscript. AT performed laboratory investigations.

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Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014

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Since October 2013, French Polynesia has experienced the largest documented outbreak of Zika virus (ZIKAV) infection. To prevent transmission of ZIKAV by blood transfusion, specific nucleic acid testing of blood donors was implemented. From November 2013 to February 2014: 42 (3%) of 1,505 blood donors, although asymptomatic at the time of blood donation, were found positive for ZIKAV by PCR. Our results serve to alert blood safety authorities about the risk of post-transfusion Zika fever.

Zika virus infection in French Polynesia: implications for blood transfusion

French Polynesia, in the South Pacific, has experienced the largest reported outbreak of ZIKAV infection, which began in October 2013, with an estimated 28,000 cases in February 2014 (about 11% of the population) [1,2], concomitantly with the circulation of dengue virus (DENV) serotypes 1 and 3 [3]. To the best of our knowledge, the occurrence of ZIKAV infection resulting from transfusion of infected blood has not been investigated. Since other arboviruses have been reported to be transmitted by blood transfusion [4], several prevention procedures were implemented in date to prevent transfusion of ZIKAV through transmission in French Polynesia, including nucleic acid testing (NAT) of blood donors. We report here the detection of ZIKAV in 42 of 1,505 blood donors, who were asymptomatic at the time of blood donation.

Background

ZIKAV, an arthropod-borne virus (arbovirus) belonging to the family *Flaviviridae* and genus *Flavivirus* [5], was first isolated in 1947 from a monkey in the Zika forest, Uganda [6]. Sporadic human Zika fever cases have been reported since the 1960s [7]. The first documented outbreak outside Africa and Asia occurred in 2007 in the Yap State, Micronesia, in the North Pacific, where Zika fever was characterised by rash, conjunctivitis and arthralgia [8].

ZIKAV has been isolated from several *Aedes* mosquito species, notably including *Ae. aegypti* [9] and *Ae. albopictus* [10]. *Ae. aegypti* is widespread in the tropical and subtropical regions of the world and *Ae. albopictus* is now established in many parts of Europe, especially Mediterranean countries [11]. Recent reports of imported cases of ZIKAV infection from south-east Asia or the Pacific to Europe [12] or Japan [13] highlight the risk of ZIKAV emergence in parts of the world where the vector is present.

Sample collection

According to the procedures of the blood bank centre of French Polynesia, all blood donors have to fill in a pre-donation questionnaire and have a medical examination before blood donation. Blood is taken only from voluntary donors who are asymptomatic at the time of donation. A signed informed consent statement was obtained from all blood donors and publication of data related to ZIKAV testing was approved by the Ethics Committee of French Polynesia (reference 66/CEPF).

ZIKAV nucleic acid testing (NAT) of samples of all donations was implemented routinely from 13 January 2014. In February, samples of donations collected from 21 November 2013 to 12 January 2014 were retrospectively tested. We report here the results of ZIKAV NAT for all donors who donated blood from 21 November 2013 to 17 February 2014.

Laboratory and clinical findings

On the basis of protocols implemented for WNV NAT [14], blood donor samples were tested in minipools. In order to increase the sensitivity of detection and to reduce the occurrence of false-negative results, sera from no more than three blood donors were included in each minipool.

Detection of Zika virus RNA in blood samples from asymptomatic donors

RNA was extracted from 200 µL minipooled or individual sera using the Easymag extraction system (bio-Mérieux, France) as previously reported [15]. ZIKAV real-time reverse-transcription PCR (RT-PCR) was performed on a CFX Biorad real-time PCR analyser using two real-time primers/probe amplification sets specific for ZIKAV [16]. The sensitivity of the assay was controlled by amplifying serial dilutions of an RNA synthetic transcript that covers the region targeted by the two primers/probe sets. A sample was considered positive when amplification showed a cycle threshold (Ct) value <38.5. However, in order to avoid false-negative results due to the pooling, each minipool showing a Ct value <40 with at least one primer/probe set was controlled by individual RT-PCR. Even if the two primers/probe sets did not react with the four DENV serotypes [16], the specificity of the amplified product from two donors whose blood was ZIKAV positive by RT-PCR was controlled by sequencing [1]. The sensitivity of the assay was the same as that previously reported (25 to 100 copies per assay) [16].

From 533 minipools tested from blood donated during 21 November 2013 to 17 February 2014, 61 were found positive, with at least one of the Ct values <40. The constitutive blood plasmas of these 61 ZIKAV-positive minipools were tested individually and revealed 34 minipools in which one of the donors was ZIKAV positive; in four minipools, two of the three donors were positive.

In total, 1,505 blood donors were tested: 42 (2.8 %) were confirmed positive by individual testing (28 with the two primer/probe sets and 14 with one primer/probe set).

The two sequenced samples were confirmed as ZIKAV (GenBank accession numbers KJ680134 and KJ680135)*, sharing 99.6% similarity with the sequence initially reported at the beginning of the outbreak (GenBank accession number KJ579442) [1].

Detection of Zika virus in culture

Sera from 34 ZIKAV RT-PCR-positive donors were inoculated on Vero cells in order to detect replicative viral particles; there was insufficient serum available for the remaining eight RT-PCR-positive donors. Of the 34 inoculated, three were positive in culture. However, the culture was conducted retrospectively and sample storage conditions were not optimal for viral culture (several freeze /thaw cycles), leading potentially to some false-negative results.

Occurrence of Zika fever-like syndrome following blood donation

Blood donors positive for ZIKAV were contacted retrospectively by telephone to investigate the occurrence

of 'Zika fever-like syndrome' (rash and /or conjunctivitis and/or arthralgia) after their blood donation. Of the 42 donors tested positive by RT-PCR, 11 declared that they had a Zika fever-like syndrome from 3 to 10 days after they gave blood.

Discussion

The main challenge in the prevention of arbovirus transfusion-derived transmission is the high rate of asymptomatic infections: this has been estimated at over 75% for DENV [17] and West Nile virus (WNV) [18]. For ZIKAV, there is no estimate available of the percentage of asymptomatic infections. Arbovirus transfusion-derived transmission has been reported principally for WNV [19], DENV [20] and chikungunya virus (CHIKV) [21,22]. For CHIKV, the risk was evaluated as high [21,22].

During the outbreaks of CHIKV infection in Italy (2007) [21] and in Réunion Island in the Indian Ocean (2005–07) [22], blood donation was discontinued and blood products were imported from blood bank centres elsewhere. In French Polynesia, due to its geographically isolated location, it was impossible to be supplied with fresh blood products from blood bank centres outside French Polynesia.

Due to the potential risk of ZIKAV transfusion-derived transmission, the need to continue blood donations and the lack of a licensed test for ZIKAV diagnosis, we decided to implement ZIKAV NAT as soon as possible, using a modified RT-PCR [16]. The protocol was implemented in November 2013, when agreement from the French Polynesian health authorities was obtained. The specificity of this RT-PCR assay has been previously evaluated and was confirmed by sequencing analysis conducted during the outbreak in French Polynesia [1] and its sensitivity was similar to that previously evaluated [16].

We detected an unexpectedly high number of positive asymptomatic blood donors (42/1,505; 3%). To date, no post-transfusion ZIKAV infection has been reported in recipients of ZIKAV-positive blood in French Polynesia; however, haemovigilance studies are still ongoing.

Due to concomitant circulation of DENV serotypes 1 and 3 since early 2013 [3], multiplex NAT testing for DENV has been implemented from April 2013: no DENV-positive donor has yet been detected. While this might be related to a low level of viraemia in asymptomatic donors, we consider it was probably due to the low level of DENV-1 and DENV-3 circulation. Pathogen inactivation of platelet concentrates using a photochemical treatment (amotosalen) of blood products and ultraviolet A light inactivation was also implemented [23].

The management of a dual outbreak of ZIKAV and DENV infection was challenging because we had to test all blood donors for both pathogens, which was time consuming and expensive. In addition, in our blood bank

centre, the mean delay between blood donation and production of fresh blood product available for transfusion is generally 24 hours. During the outbreaks, the mean delay was three days.

This report serves as a reminder of the importance of quickly adapting blood donation safety procedures to the local epidemiological context. Moreover, it should help in anticipating the needs in other parts of the Pacific region, such as in New Caledonia (South Pacific), where an outbreak of ZIKAV infection started in February 2014 [24].

Our findings suggest that ZIKAV NAT should be used to prevent blood transfusion-transmitted ZIKAV. As recommended by the European Centre for Disease Prevention and Control, blood safety authorities need to be vigilant and should consider deferral of blood donors returning from areas with an outbreak of ZIKAV infection [2]. In areas endemic for *Aedes* species, a preparedness plan to respond to future outbreaks of ZIKAV infection should include emergency plans to sustain blood supply.

Conflict of interest

None declared.

Authors' contributions

Didier Musso (DM), Tuxuan Nhan (TN), Emilie Robin (ER), Damien Bierlaire (DB), Van-Mai Cao-Lormeau (VM CL) and Julien Broult (JB) wrote the manuscript. Claudine Roche (CR), Karen Zisou (KZ) and Aurore Shan Yan (A SY) performed laboratory investigations.

* Addendum:

The GenBank accession numbers of the two ZIKAV sequences, derived from the amplified PCR products from two blood donors whose blood was ZIKAV positive by RT-PCR, were added on 11 April 2014.

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<http://www.ncipd.org/>

CYPRUS

Newsletter of the Network for Surveillance and Control of Communicable Diseases in Cyprus
Medical and Public Health Services, Ministry of Health, Nicosia
Biannual, print and online. In Greek.
<http://www.moh.gov.cy>

CZECH REPUBLIC

Zpravy CEM (Bulletin of the Centre of Epidemiology and Microbiology)
Centrum Epidemiologie a Mikrobiologie Státního Zdravotního Ústavu, Prague
Monthly, print and online. In Czech, titles in English.
<http://www.szu.cz/cema/adefaultt.htm>

EPIDAT (Notifications of infectious diseases in the Czech Republic)
<http://www.szu.cz/cema/epidat/epidat.htm>

DENMARK

EPI-NEWS
Department of Epidemiology, Statens Serum Institut, Copenhagen
Weekly, print and online. In Danish and English.
<http://www.ssi.dk>

FINLAND

Kansanterveyslaitos
Department of Infectious Disease Epidemiology, National Public Health Institute, Helsinki
Monthly, print and online. In Finnish.
http://www.ktl.fi/portal/suomi/osastot/infe/tutkimus/tartuntatautien_seuranta/tartuntatautilaakarin_kommentit/

FRANCE

Bulletin épidémiologique hebdomadaire
Institut de veille sanitaire, Saint-Maurice Cedex
Weekly, print and online. In French.
<http://www.invs.sante.fr/beh/default.htm>

GERMANY

Epidemiologisches Bulletin
Robert Koch-Institut, Berlin
Weekly, print and online. In German.
http://www.rki.de/DE/Content/Infekt/EpidBull/epid__bull__node.html

GREECE

HCDCP Newsletter
Hellenic Centre for Disease Control and Prevention (HCDCP/KEELPNO), Athens
Monthly, online. In English and Greek.
<http://www2.keelpno.gr/blog/?lang=en>

HUNGARY

Epinfo (az Országos Epidemiológiai Központ epidemiológiai információs hetilapja)
National Center For Epidemiology, Budapest
Weekly, online. In Hungarian.
<http://www.oek.hu/oek.web?to=839&nid=41&pid=7&lang=hun>

ICELAND

EPI-ICE
Landlæknisembættið
Directorate Of Health, Seltjarnarnes
Monthly, online. In Icelandic and English.
<http://www.landlaeknir.is>

IRELAND

EPI-INSIGHT
Health Protection Surveillance Centre, Dublin
Monthly, print and online. In English.
<http://www.hpsc.ie/hpsc/EPI-Insight>

ITALY

Notiziario dell'Istituto Superiore di Sanità
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome
Monthly, online. In Italian.
<http://www.iss.it/publ/noti/index.php?lang=1&tipo=4>

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Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome
Monthly, online. In Italian.
<http://www.epicentro.iss.it/ben>

LATVIA

Epidemiologijas Biļeteni
Sabiedrības veselības agentūra
Public Health Agency, Riga
Online. In Latvian.
<http://www.sva.lv/epidemiologija/bileteni>

LITHUANIA

Epidemiologijos žinios
Užkrečiamųjų ligų profilaktikos ir kontrolės centras
Center for Communicable Disease Prevention and Control, Vilnius
Online. In Lithuanian.
<http://www.ulac.lt/index.php?pl=26>

NETHERLANDS

Infectieziekten Bulletin
Rijksinstituut voor Volksgezondheid en Milieu
National Institute of Public Health and the Environment, Bilthoven
Monthly, print and online. In Dutch.
<http://www.rivm.nl/infectieziektenbulletin>

NORWAY

MSIS-rapport
Folkehelseinstituttet, Oslo
Weekly, print and online. In Norwegian.
<http://www.folkehelse.no/nyhetsbrev/msis>

POLAND

Meldunki o zachorowaniach na choroby zakaźne i zatruciach w Polsce
Panstwowy Zakład Higieny,
National Institute of Hygiene, Warsaw
Fortnightly, online. In Polish and English.
<http://www.pzh.gov.pl>

PORTUGAL

Saúde em Números
Ministério da Saúde,
Direcção-Geral da Saúde, Lisbon
Sporadic, print only. In Portuguese.
<http://www.dgs.pt>

ROMANIA

Info Epidemiologia
Centrul pentru Prevenirea și Controlul Bolilor Transmisibile, National Centre
of Communicable Diseases Prevention and Control, Institute of Public Health,
Bucharest
Sporadic, print only. In Romanian.
Sporadic, print only. In Romanian.
http://www.insp.gov.ro/cnscbt/index.php?option=com_docman&Itemid=12

SLOVENIA

CNB Novice
Inštitut za varovanje zdravja, Center za nalezljive bolezni, Institute of Public
Health, Center for Infectious Diseases, Ljubljana
Monthly, online. In Slovene.
<http://www.ivz.si>

SPAIN

Boletín Epidemiológico Semanal
Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid
Fortnightly, print and online. In Spanish.
<http://revista.isciii.es>

SWEDEN

Smittskyddsinstitutets nyhetsbrev
Smittskyddsinstitutet, Stockholm
Weekly, online. In Swedish.
<http://www.smittskyddsinstitutet.se>

UNITED KINGDOM

ENGLAND AND WALES

Health Protection Report
Health Protection Agency, London
Weekly, online only. In English.
<http://www.hpa.org.uk/hpr>

NORTHERN IRELAND

Communicable Diseases Monthly Report
Communicable Disease Surveillance Centre, Northern Ireland, Belfast
Monthly, print and online. In English.
<http://www.cdscni.org.uk/publications>

SCOTLAND

Health Protection Scotland Weekly Report
Health Protection Scotland, Glasgow
Weekly, print and online. In English.
<http://www.hps.scot.nhs.uk/ewr/>

EUROPEAN UNION

“Europa” is the official portal of the European Union. It provides up-to-date
coverage of main events and information on activities and institutions of the
European Union.
<http://europa.eu>

EUROPEAN COMMISSION - PUBLIC HEALTH

The website of European Commission Directorate General for Health and
Consumer Protection (DG SANCO).
<http://ec.europa.eu/health/>

HEALTH-EU PORTAL

The Health-EU Portal (the official public health portal of the European Union)
includes a wide range of information and data on health-related issues and
activities at both European and international level.
<http://ec.europa.eu/health-eu/>

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

European Centre for Disease Prevention and Control (ECDC)
The European Centre for Disease Prevention and Control (ECDC) was
established in 2005. It is an EU agency with aim to strengthen Europe's
defences against infectious diseases. It is seated in Stockholm, Sweden.
<http://www.ecdc.europa.eu>

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