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Note from the editors: Articles on Zika preparedness

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Summer has come to Europe and with it the holiday season for many. With the sunshine and warmer temperatures comes pleasure but also a nuisance in form of invasive and non-invasive mosquitoes. It is no news to our readers that in some parts of Europe, in particular in the Mediterranean basin, *Aedes albopictus* mosquitoes have become established over the past decades [1].

Already earlier this year, in light of the emergence of Zika virus in South America and the Caribbean in late 2015, questions were raised about the risk for Europe. Findings that *Ae. albopictus*, even though less competent than *Ae. aegypti*, can be a potential vector for Zika virus transmission [2,3] have further fuelled the concerns of possible importation of Zika virus, also in light of the upcoming Olympic and Paralympic Games in Brazil, a country with a large Zika virus disease epidemic. The European Centre for Disease Prevention and Control (ECDC) has addressed concerns related to disease occurrence in connection with travel to the Games in Brazil in a recent risk assessment [4]. It concluded that visitors to Rio de Janeiro, Brazil, will be most at risk of gastrointestinal illness and vector-borne infection. However, given that the Games will take place during the winter season in Rio, when mosquito populations will be reduced, the risk of imported mosquito-borne infections such as Zika vrus disease, dengue and chikungunya is expected to be very low [4]. An article from EuroTravNet, published in *Eurosurveillance* last week, supported these conclusions based on observations in travellers returning from Brazil between June 2013 and May 2016 [5].

Preparedness is essential to address potential introduction and onward transmission in Europe of Zika virus and of other arboviruses, such as dengue and chikungunya viruses, transmitted by the same vectors. In this issue of *Eurosurveillance*, three articles supply evidence about Zika virus transmission dynamics and describe experiences that can support ongoing preparedness activities.

Rojas et al. provide insight into the transmissibility and epidemiology of Zika virus in Colombia from the early stages of the outbreak in the country [6]. Little has been published on the basic reproduction number (R_0) of Zika virus transmission so far. Rojas et al. estimated R_0 based on data from two different settings: (i) a middle-sized municipality with tropical climate on the mainland; and (ii) a densely populated island [6]. For the latter R_0 was 1.41 (95% confidence interval (CI): 1.15–1.74), lower than that for the municipality on the continent, 4.61 (95% CI: 4.11–5.16). The authors considered that the more reliable estimate was the one obtained from the island setting. Both estimates confirm the epidemiological picture of continuous rapid spread seen in the affected countries of South America and the Caribbean. Notably, the authors found a higher attack rate in women, without clear indication that this finding was due to testing or information bias.

The other two articles come from French overseas Territories of America (FTA) and Réunion, a French department in the Indian Ocean. Both draw on lessons learnt from earlier arbovirus epidemics (chikungunya and dengue) that had considerable impact on the health of citizens and put a strain on the public health systems. Daudens-Vaysse et al. share experiences and results from the epidemiological surveillance set up in the FTA at the beginning of the epidemic, covering the period from November 2015 to February 2016 [7]. They highlight challenges associated with the chosen case definition, namely the absence of rash, the foundation of their case definition, in a significant proportion of patients. Larrieu et al. describe surveillance and response systems and tools adapted in Réunion to different epidemiological phases including a potential epidemic [8]. The example of the recent early detection of two imported cases and the measures taken to prevent onward transmission illustrates the major strengths of the system put in place: a powerful vector control team and close interdisciplinary collaboration between various players including the public health authorities.

We hope our readers will find the papers interesting and the experiences relevant to Europe and also island settings facing possible emergence of Zika virus.

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Réunion Island prepared for possible Zika virus emergence, 2016

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Zika virus (ZIKV) has recently spread widely and turned into a major international public health threat. Réunion appears to offer conditions particularly favourable to its emergence and therefore prepared to face possible introduction of the virus. We designed a scaled surveillance and response system with specific objectives, methods and measures for various epidemiological phases including a potential epidemic. Several tools were developed in order to (i) detect individual cases (including a large information campaign on the disease and suspicion criteria), (ii) monitor an outbreak through several complementary systems allowing to monitor trends in disease occurrence and geographic spread and (iii) detect severe forms of the disease in collaboration with hospital clinicians. We put the emphasis on detecting the first cases in order to contain the spread of the virus as much as possible and try to avoid progress towards an epidemic. Our two main strengths are a powerful vector control team, and a close collaboration between clinicians, virologists, epidemiologists, entomologists and public health authorities. Our planned surveillance system could be relevant to Europe and island settings threatened by Zika virus all over the world.

Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus transmitted by *Aedes* spp. mosquitoes. It was first isolated in 1947 from a sentinel Rhesus monkey in Uganda [1], and shortly hereafter it was shown to cause human infections [2,3]. During sixty years, its area of distribution has been restricted to Africa and Asia where it has been recognised to be a cause of febrile illness in humans with symptoms including fever, headache, conjunctivitis, myalgia, rash, joint pains [4,5]. In 2007, it spread outside its usual geographic range for the first time, and caused an outbreak on Yap Island in the Federated States of Micronesia [4]. Most infected persons were asymptomatic or had a mild disease. Therefore, despite an attack rate of 73%, international authorities and the media paid little attention to this event.

However, this emergence of ZIKV outside Africa and Asia was a warning signal of its potential to spread to other Pacific islands and the Americas [5]. In 2013–14, the virus continued its geographical expansion and caused large outbreaks in the western Pacific region, including French Polynesia, New Caledonia, Easter Island, and the Cook Islands [6-9]. International concern was raised when the virus was suspected to be associated with a 20-fold increase of Guillain-Barré syndrome (GBS) incidence in French Polynesia [10]. In 2015, ZIKV reached the Americas. After ZIKV emerged in Brazil, an increase in suspected microcephaly cases and other fetal anomalies was observed and thought to be associated with ZIKV infection during pregnancy. This caused Brazil to declare Zika a public health emergency of national importance in November 2015 [11].

In just three years, a virus considered benign turned into a major public health threat because of its impressive capacity to spread out rapidly, the associated high attack rates and its ability to cause severe illness. In that context, the World Health Organization (WHO) encouraged countries at risk to be prepared for ZIKV emergence in terms of diagnosis, surveillance and vector control [12]. On 1 February 2016, following a meeting of its 'International Health Regulations (2005)

Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations', WHO declared that the ZIKV epidemic, constitutes a Public Health Emergency of International Concern (PHEIC) [13].

Réunion, a French overseas administrated territory with 830,000 inhabitants located in the south-western Indian Ocean, faced a similar arbovirus threat in 2006–07. A hardly known arbovirus called chikungunya virus, considered as benign at the time, emerged on the island and caused the largest epidemic ever described with an attack rate of 34% [14] and occurrence of unexpected severe forms, which led to a major health and social crisis. Ten years later, Réunion appears to offer conditions particularly favourable to emergence of ZIKV. Indeed, ZIKV circulation has never been documented in Réunion and therefore immunity may be very low, or even non-existent in the general population. The main vector for Zika virus is *Aedes agypti*, however, *Ae. albopictus*, abundant throughout the year in all inhabited areas of the island was also described as a competent vector of ZIKV [15,16]. Therefore, Réunion prepared for possible ZIKV emergence by implementing a surveillance system in order to limit the risk of spread on the whole island.

The aim of this paper is to describe the tools set up in Réunion in order to face a potential emergence of ZIKV within the next few months.

Overview of the surveillance and response system

Réunion benefits from a healthcare system similar to mainland France with more than 890 general practitioners and 80 paediatricians distributed throughout the island, 59 laboratories, three public and 56 private, as well as four hospitals and six emergency departments.

In November 2015, a specific surveillance system of ZIKV infections was implemented on Réunion by the regional unit (Cire OI) of the French national public health agency (Santé publique France) in collaboration with the French Health Agency Indian Ocean (ARS OI). It is based on current knowledge about ZIKV and past experience with chikungunya and dengue surveillance and control and follows the WHO recommendation [12]. We designed a scaled surveillance and response system with specific objectives, methods and measures for various epidemiological phases including a potential epidemic (Figure 1).

The focus is on three surveillance objectives:

(i) To detect individual cases at any time, except during an outbreak;

(ii) To monitor the outbreak i.e. to follow trends in disease occurrence and document the health impact;

(iii) To detect and describe severe forms of the disease.

Detection of individual cases

The general organisation of the surveillance system implemented to detect all ZIKV cases is presented in Figure 2. Surveillance is based on the notification by the reference laboratory and health practitioners of any suspected and confirmed cases of ZIKV.

A patient has to meet both clinical and epidemiological criteria to be considered as a suspected case:

(i) Clinical criteria: patient presenting with maculopapular rash with or without fever AND at least two additional symptoms (conjunctivitis/arthralgia/myalgia);

(ii) Epidemiological criteria: travel in an area affected by ZIKV circulation within the two weeks preceding clinical symptoms; any temporo-spatial cluster of patients meeting the clinical criteria.

A probable case is a suspected case with presence of IgM antibody against Zika virus and an epidemiological link with any confirmed case.

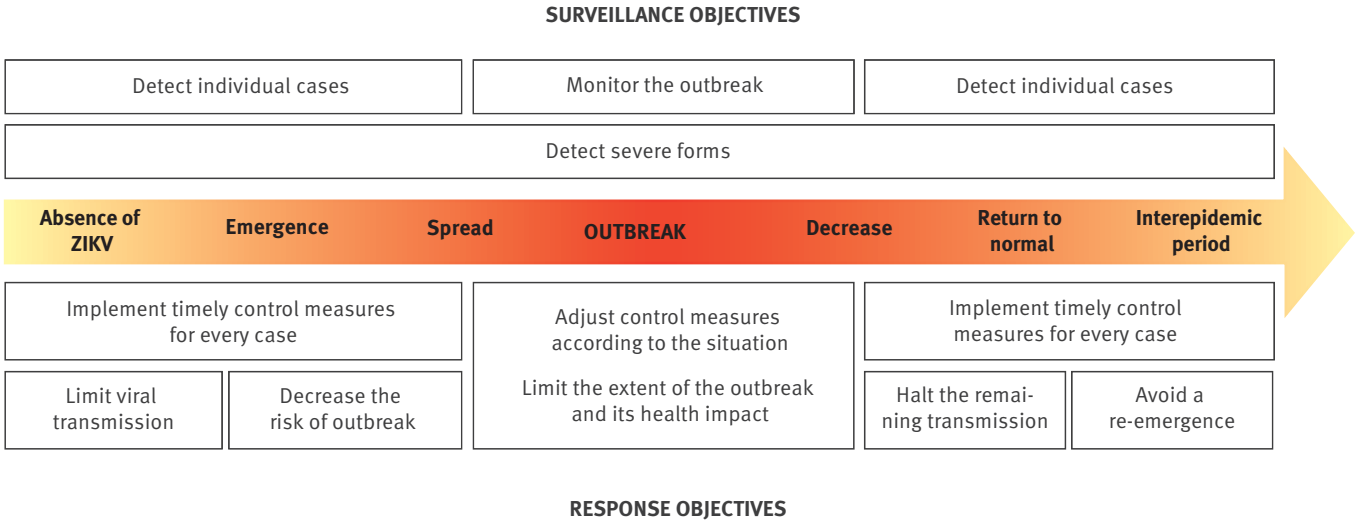
A confirmed case is a person with laboratory confirmation of recent Zika virus infection i.e. positive reverse transcriptase (RT)-PCR in serum or other sample or positive seroneutralisation assay and exclusion of other flaviviruses.

The Regional and National Reference Laboratories for Arboviruses perform the laboratory diagnosis of Zika virus infection. It is based on the direct detection of viral genome by RT-PCR on serum from day 0 to 5 after symptom onset and on urine until day 15 after symptom onset. The detection of IgM and IgG anti-Zika on serum from day 5 after the onset of symptoms is complicated by the frequency of cross-reactions with other flaviviruses such as dengue virus. The detection of antibodies could be confirmed by seroneutralisation assay to determine the specificity of the detected antibodies. Suspected cases should also be tested for dengue and chikungunya as both these arboviruses could emerge or re-emerge in Réunion.

As soon as a case is notified, after a brief assessment by the Cire OI, control measures are immediately implemented by the vector control team. They comprise the elimination of peri-domiciliary breeding sites of *Aedes* mosquitoes, spraying, health education, and active door-to-door case finding. Considering expected *Ae. albopictus* area of activity, such control measures are performed in a 100 m radius around the residence of the case (i.e. the expected radius of activity of the mosquito) and around any subsequent suspect cases identified during the case finding. They can also be implemented around the worksite, or any place where cases declared having spent time or been exposed to mosquitoes. An entomologic surveillance using house and Breteau indexes [17] is routinely performed through control of a random sample of almost 50,000 houses per year i.e. 15% of the total dwellings of the island.

Figure 1

Objectives of Zika virus surveillance and response according to the epidemiological situation, Réunion, 2016



ZIKV: Zika virus.

In parallel, exercises are performed in order to check effectiveness of control measures on vector densities.

As this surveillance is based on detection of suspect cases by general practitioners (GPs), we undertook an information campaign in order to raise their awareness of ZIKV and its potential emergence. A document was delivered in person to all the GPs on the island, focusing on the disease (clinical signs, transmission and laboratory diagnosis) and including an epidemiological report presenting the international situation, the risk for Réunion and recommendations on case detection. Updated versions of this document are sent by email and can be uploaded from the ARS webpage. We also organised numerous specific meetings with the medical staff of intensive care units as well as emergency, gynaecology, and infectious diseases departments.

Furthermore, this information was relayed by the media in order to inform the general population, and especially travellers returning from an epidemic area. A poster was displayed at the airport, presenting symptoms associated with ZIKV infection and recommending people returning from an affected area to visit a doctor in case of any of these symptoms.

In case of laboratory confirmation of an autochtonous case, all GPs of the affected area(s) are immediately called by phone in order to enhance their vigilance and promptness of case notification.

When autochthonous transmission of ZIKV is identified on the island, the objective of surveillance remains the same i.e. to detect all the cases in order to implement individual control measures. The organisation of the surveillance systems and the control measures remain unchanged. However, in this instance, all inhabitants of Réunion meet the epidemiological criteria of the case definition and suspicion is based on clinical criteria only.

Monitoring the outbreak

During the outbreak phase, laboratory confirmation of each individual case and implementation of control measures around each case are no longer efficient nor feasible. Therefore, surveillance shifts to a sentinel monitoring of trends in disease occurrence and the geographic spread, based on several complementary surveillance systems: (i) a network of sentinel general practitioners, (ii) online self-reported symptoms surveillance, (iii) concern about Zika on social media, (iv) syndromic surveillance of emergency department consultations, (v) mortality surveillance. Control measures are guided by epidemiological surveillance, with more vector control teams in the most affected areas in order to limit local transmission of the virus.

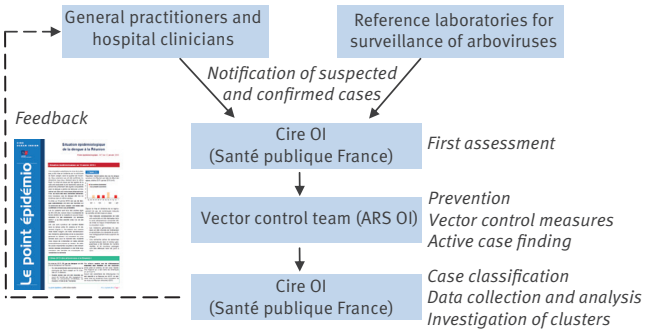
Sentinel practitioners network

On Réunion, a sentinel network, consisting of 50 GPs scattered across the island and representing 6.2% of the GPs on Réunion, is operational since 1996 and conducts surveillance of influenza, gastroenteritis and varicella [18]. On a weekly basis, they report the number of consultations for these syndromes.

This network can be rapidly mobilised to monitor other diseases with an epidemic potential, and has already shown its responsiveness and reliability for surveillance during outbreaks of chikungunya in 2005–06 [14], pandemic influenza A(H1N1) in 2009 [19], gastroenteritis in 2012 [20] and conjunctivitis in 2015 [21]. This network will be activated for the surveillance of suspected cases of ZIKV infections in case of an

Figure 2

General organisation of the surveillance system to detect individual ZIKV cases, Réunion, 2016



ARS OI: French Health Agency Indian Ocean; Cire OI: Regional unit of the French national public health agency (Santé publique France)

outbreak in Réunion, and the total number of symptomatic ZIKV cases can be estimated on a weekly basis.

Online self-reported symptoms surveillance

The ARS OI implemented in April 2014 a web-based surveillance system called 'Koman i lé', that allows to follow perceived health among people who do not systematically visit their GP. Individual volunteers aged over 18 weekly fill in a short survey asking symptoms presented during the previous week. An indicator for ZIKV infection has been constructed based on clinical criteria previously presented: rash with or without fever AND at least two additional symptoms (conjunctivitis/arthralgia/myalgia). The total number and proportion of participants reporting ZIKV symptoms can be monitored on a weekly basis, for the whole island and according to place of residence.

Concern about Zika virus on social media

Several studies suggest that social media could be useful to monitor epidemics of infectious diseases [22]. Sick people notably talk on Twitter about their health conditions, their feelings about the symptoms, and treatments they take to relieve the symptoms. In that context, a tool was developed to monitor tweets concerning Zika posted by Réunion dwellers. Tweets mentioning the keyword 'Zika' are collected using an R programme from the free Twitter public application programming interface (API), which allows individuals to request a feed of public tweets matching specific search criteria. Then, usernames are removed in order to anonymise the tweets. Duplicate tweets and retweets (tweets posted by one user and then forwarded by another user) are removed. Then, the weekly number of tweets concerning Zika on the island can be obtained and monitored such as other surveillance indicators. Text mining can also be performed in order to explore qualitatively the concern of the population. The goal of this surveillance is to measure the concern of the population about Zika virus, which could be associated with the real incidence of the disease.

Emergency department consultations

Réunion has a syndromic surveillance system based on all four emergency departments (ED) of the island (Organisation de la surveillance coordonnée des urgences (OSCOUR) network). Data are collected each day directly from the patients' computerised medical files that are filled in during medical consultations at the ED. Each morning, data are downloaded and analysed by an epidemiologist of the Cire OI. The diagnoses are classified according to the 10th revision of the International Classification of Diseases (ICD-10) [23]. The risk of emergence of Zika virus was recently discussed with the staff of the four EDs of the island. In case of emergence, specific meetings will immediately be organised in order to increase awareness, and remind healthcare workers about the case definition and ICD-10 classification code for suspicion of ZIKV.

Zika virus-associated and all-cause mortality

In case of an outbreak, the total number and excess of deaths from all causes will be analysed on a weekly basis in order to detect a potential increase. This system will be completed by analysis of all death certificates received by the regional public health authority that mention 'Zika'.

Surveillance of severe cases

Based on current knowledge on severe forms potentially associated with ZIKV infection [10,24], two specific systems were implemented: (i) surveillance of GBS and other neurological disorders and (ii) surveillance of microcephaly cases and other fetal anomalies, to monitor the number of cases, to describe the patients and their evolution, and to detect any emerging severe form of the disease. The observed number of cases will be compared with the expected number to determine whether a significant increase is observed.

All suspicions of severe cases will lead to laboratory investigations of serum and urine in order to document ZIKV infection by RT-PCR, detection of antibodies and seroneutralisation assay. RT-PCR will also be performed on cerebrospinal fluid for GBS and other neurological diseases, and on amniotic fluid and fetal tissues (in case of fetal loss) for fetal anomalies.

Surveillance of Guillain-Barré syndrome and other neurological forms

A specific surveillance system has been developed with hospital clinicians from departments likely to hospitalise such patients: adult and paediatric intensive care units, infectious diseases and neurology departments. All cases of GBS and other potential neurological complications (meningo-encephalitis, myelitis, etc.) will be notified in real time to the Cire OI through a specific form. Collected data will include: socio-demographic information, comorbidities, type of neurological disease, symptoms of ZIKV infection during the previous weeks, laboratory results, length of hospitalisation and evolution. The number of expected GBS cases has been estimated using hospital databases. From 2010

to 2014, the mean number of yearly reported cases was 17, the median was 20 and the median number of monthly cases ranged from 0 to 5 without variations between the rainy and the dry season.

Surveillance of microcephaly and other fetal anomalies

On Réunion, suspicions of microcephaly or other fetal anomaly detected by ultrasound are systematically referred to one of the two prenatal diagnostic centres of the island. All cases of microcephaly (head circumference under three standard deviations expected for gestation) and/or other brain anomaly potentially linked to ZIKV infection (i.e. in absence of another clearly identified aetiology) will be notified in real time to the Cire OI. Collected data will include: socio-demographic information, comorbidities, type of anomaly, symptoms of ZIKV infection during pregnancy, laboratory results and outcome of pregnancy. Data from the registry of congenital anomalies will also be analysed on a monthly basis in order to detect any increase in microcephaly or other congenital anomalies. The number of expected microcephaly has been estimated using the Eurocat website database [25]. From 2002 to 2012, 56 microcephaly cases were reported on Réunion (average of 8 cases per year, i.e. 3.5 per 10,000 pregnancies). According to those data, the number of expected microcephaly per year is five. As the database showed a non-significant increase of the reported cases in the most recent years, a new estimation was made using data from 2008 to 2012. According to the most recent reports, the number of expected microcephaly on Réunion is eight per year.

Discussion

When ZIKV emerged in Brazil, modelling anticipated a significant international spread by travellers to the rest of the Americas, Europe, and Asia [26]. Spread in the Americas is ongoing [27], revealing the explosive pandemic potential of ZIKV. It can be expected that it will emerge soon in other areas of the world and notably in the Indian Ocean. Taking advantage of its unfortunate history of the CHIKV outbreak, Réunion prepared to face a ZIKV emergence within the next months. A surveillance system was implemented to be able to detect the introduction of ZIKV at an early stage and to monitor the spread and impact of the infections in order to guide the implementation of control measures.

Réunion belongs to a regional network for epidemiological surveillance and health alert management coordinated by the Indian Ocean Commission, an intergovernmental organisation including Madagascar, Comoros, Mauritius and Seychelles. All information regarding preparation for ZIKV emergence is shared as part of this network. In case of clinical suspicions in a member country, cooperation can be undertaken for epidemiological investigations and laboratory diagnostics.

Limitations

Although surveillance of ZIKV has been planned ahead and is based on solid experience and networks [18], some limits can be anticipated. The beginning of the outbreak phase can be demanding for surveillance, particularly when the number of cases cannot be counted anymore but needs to be estimated through GP consultations. Indeed, estimations can lack reliability if the total number of cases remains limited. In such instance, additional GPs will be recruited temporarily in order to improve coverage of the sentinel network, as it was done in 2007 during the chikungunya outbreak. Indeed, some doctors do not want to enrol in the network on long-term basis but volunteer for a temporary participation in case of a specific health event. Also, the suitability of data generated by monitoring Twitter is quite uncertain and will depend on the number of active users of this social network. Work is underway to extend surveillance to other tools more commonly used in Reunion Island, such as Facebook which is particularly popular. Mortality surveillance could lead to over-reporting in case of a large outbreak. The surveillance indicator will be the number of death certificates mentioning the word ‘Zika’, rather than ‘death associated with Zika’; and a clear communication will be essential in order to explain that not all deaths in those infected can be directly attributed to ZIKV infection.

Conclusions

A large outbreak could have severe effects on the healthcare system and public health infrastructure and would potentially affect general functions of society. Therefore, surveillance and control of ZIKV infections are being anticipated with emphasis on detecting the first cases in order to contain the spread of the virus as much as possible and try to avoid progress towards an epidemic. With this in mind, our two main strengths are:

(i) A powerful vector control team: following the chikungunya outbreak, 150 staff have been employed and trained to fight against arboviruses. They also convey prevention messages and perform active case finding of suspect cases among a large perimeter around every confirmed cases. Considering the subclinical nature of the infection by ZIKV, this active door-to-door case finding is a major asset for early detection of spatio-temporal clusters.

(ii) A close collaboration between clinicians, virologists, epidemiologists, entomologists and public health authorities. Indeed, the 2005–06 chikungunya epidemic led to a major health and social crisis in 2006, and all the local health professionals are conscious of the threat and of the necessity to detect and report the first cases.

Our surveillance system could be relevant to Europe and island settings threatened by Zika virus all over the world. Recently we had the opportunity to test this surveillance system and to show its reactivity and

effectiveness. Early March, a traveller returned from Martinique on a Saturday morning with fever, rash and arthralgia. About one hour later, they were seen by a clinician who suspected ZIKV infection, initiated laboratory test for confirmation and immediately informed the ARS and the Cire OI. The first control measures around the patient could be undertaken without delay, including confinement and individual protection against mosquito bites. During the following days, peri-domiciliary elimination of breeding sites and spraying was also performed. In April, a second imported case was also detected and confirmed very early. No secondary case was detected or reported despite an active research of symptomatic patients. The surveillance system, and notably information given to health professionals, allowed a timely detection of these cases, and the risk of dissemination was considerably decreased by implementation of immediate control measures.

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Conflict of interest

None declared

Authors' contributions

SL wrote the manuscript. LF, OR, CD, TA, HT, EB, FP, PV, EA, DV, PP, MPM, PVT, FC, AG, HDV and FB took part in alert and surveillance systems of Zika. MCJB and ILG collaborated in molecular biology techniques. All authors participated in the preparation of Zika surveillance. All authors read and approved the final manuscript.

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Zika emergence in the French Territories of America and description of first confirmed cases of Zika virus infection on Martinique, November 2015 to February 2016

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Following of the emergence of Zika virus in Brazil in 2015, an epidemiological surveillance system was quickly implemented in the French overseas Territories of America (FTA) according to previous experience with dengue and chikungunya and has detected first cases of Zika. General practitioners and medical microbiologists were invited to report all clinically suspected cases of Zika, laboratory investigations were systematically conducted (RT-PCR). On 18 December, the first autochthonous case of Zika virus infection was confirmed by RT-PCR on French Guiana and Martinique, indicating introduction of Zika virus in FTA. The viral circulation of Zika virus was then also confirmed on Guadeloupe and Saint-Martin. We report here early findings on 203 confirmed cases of Zika virus infection identified by RT-PCR or seroneutralisation on Martinique Island between 24 November 2015 and 20 January 2016. All cases were investigated. Common clinical signs were observed (maculopapular rash, arthralgia, fever, myalgia and conjunctival hyperaemia) among these patients, but the rash, the foundation of our case definition, may be absent in a significant proportion of patients (16%). These results are important for the implementation of a suspected case definition, the main tool for epidemiological surveillance, in territories that may be affected by ZIKV emergence, including Europe.

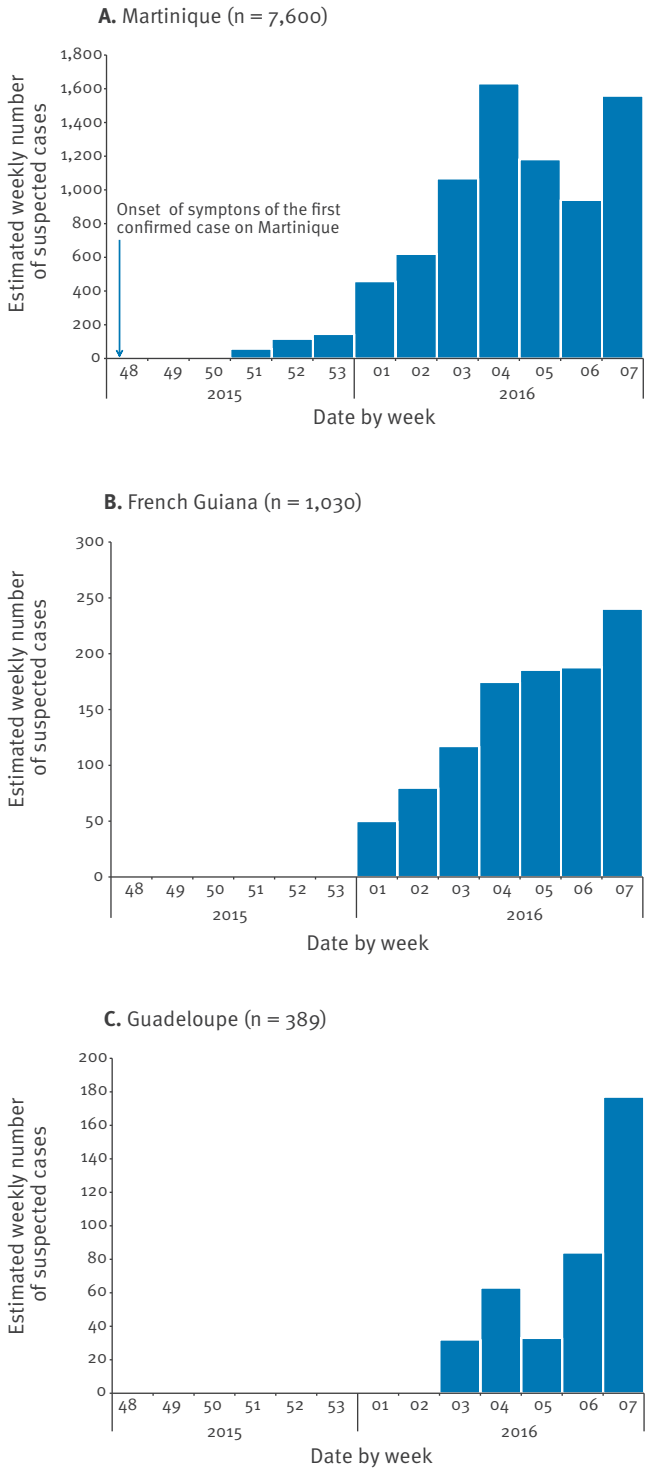
Introduction

Zika virus (ZIKV) is a Flavivirus related to dengue, yellow fever and West Nile viruses, mainly transmitted by *Aedes* mosquitoes [1,2].

In May 2015, the World Health Organization (WHO) reported the first local transmission of ZIKV in the north east of Brazil [3]. On 1 December 2015, Brazil confirmed ZIKV autochthonous circulation. By February 2016, the Brazilian Ministry of Health estimated that 500,000 to 1,500,000 suspected cases of ZIKV disease have occurred, and 20 countries or territories in the Americas have reported autochthonous ZIKV circulation [4,5].

Figure 1

Estimated weekly number of suspected Zika cases reported by general practitioners, 23 November 2015–25 February 2016



A possible association of ZIKV infection with post-infectious Guillain–Barré Syndrome (GBS) and with adverse pregnancy outcomes was noted in Brazil and French Polynesia and raised awareness for these phenomena in all affected territories [6,7].

On Martinique island, a territory of 390,000 inhabitants in the French West Indies, a family cluster of three cases of eruptive disease (rash and/or fever) was reported to the Health Agency of Martinique on 4 December 2015 by a medical laboratory and a paediatrician. Given the epidemiological situation in South America and the Caribbean, it was decided to test for of dengue, chikungunya and Zika virus. On 14 December 2015, the French National Reference Centre for Arboviruses (NRC) in Marseille, France, confirmed ZIKV by serology in one member of the household (positive for anti-Zika IgM and anti-*Flavivirus* IgG). Because of the endemic circulation of dengue virus in Martinique with high transmission in August to February, this result could not confirm recent ZIKV infection but only recent infection to *Flavivirus,* and a seroneutralisation was implemented. On 30 December 2015, the NRC reported that seroneutralisation was positive, confirming a ZIKV infection in the initial cluster. This was the first autochthonous case detected in the French overseas territories of America (FTA) with a date of symptom onset on 24 November 2015. On 18 December, the laboratory of virology of the University Hospital of Martinique confirmed a ZIKV infection by RT-PCR in a person not connected to the family cluster and who had not travelled.

On 18 December, the first autochthonous case was confirmed in Saint Laurent du Maroni in French Guiana by RT-PCR at the National Reference Centre for Arboviruses, Influenza virus and Hantavirus at the Institut Pasteur of French Guiana. On 15 January, a first positive RT-PCR for ZIKV was reported both in Saint Martin and in Guadeloupe.

This article describes the surveillance system in FTA and presents a clinical description of all confirmed ZIKV cases in Martinique from the first identified case to the date when laboratory confirmation of individual cases was stopped on 20 January 2016.

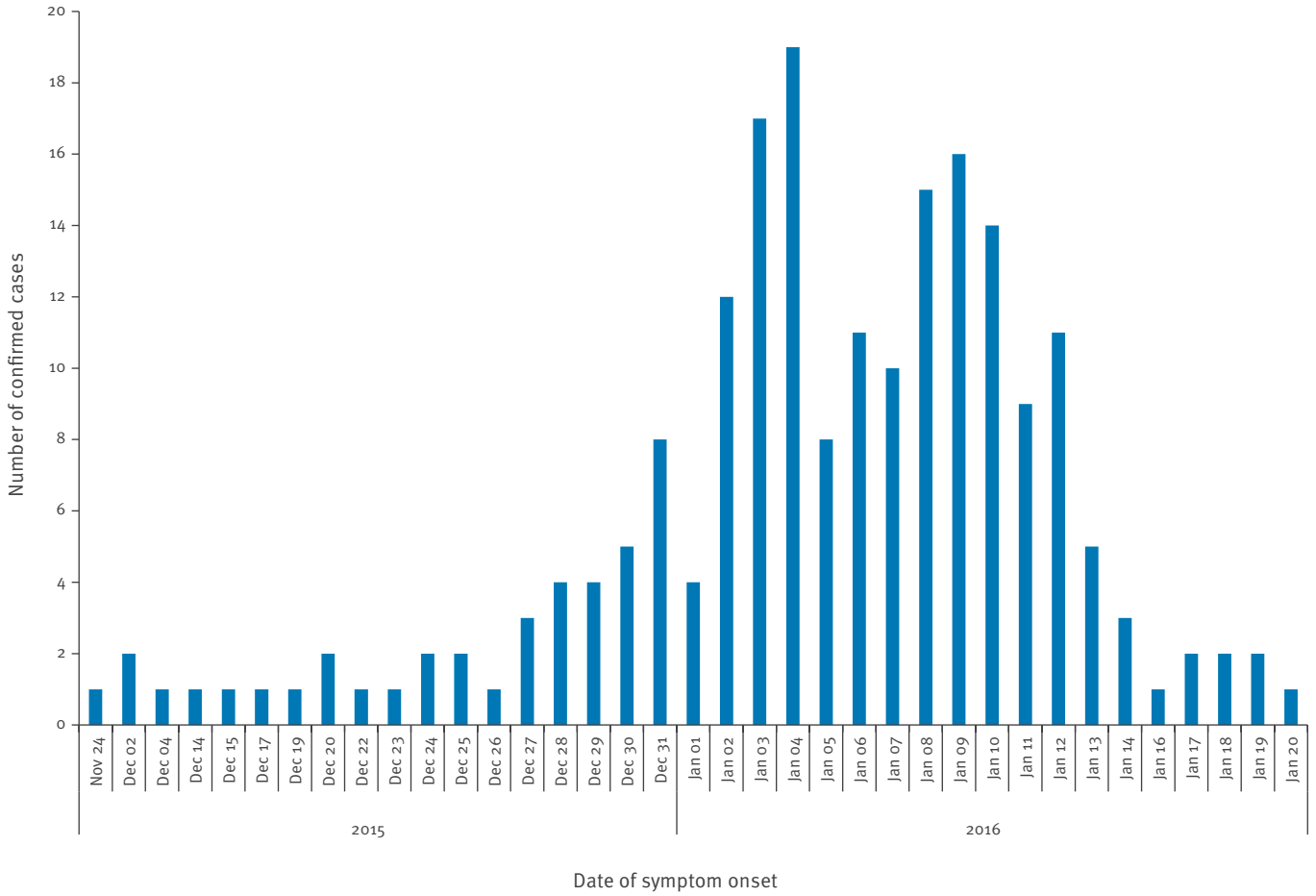
Surveillance system in the French overseas territories of America: French Guiana, Guadeloupe, Martinique, Saint Barthélemy and Saint Martin

In response to dengue outbreaks which are occurring in this area and to the emergence of chikungunya in 2013, each FTA implemented action plans ('Programme de Surveillance, d'Alerte et de Gestion' (Psage)), based on the Integrated Management Strategy recommended by the WHO for dengue [8]. These plans include four phases of increasing epidemic risk. A similar plan was immediately applied to the risk of Zika emergence when the alert for Brazil was launched.

In the pre-emergence phase (phase 1), the surveillance aims to detect early and to laboratory-confirm the introduction of the virus. Therefore, general practitioners (GPs) and medical microbiologists are invited to report all clinically suspected cases of Zika. A suspected case is defined as any individual with sudden onset of maculopapular rash with or without fever associated with

Figure 2

Confirmed cases of Zika virus infection by date of onset, Martinique, 24 November 2015–20 January 2016 (n = 203)



at least two of the three signs conjunctival hyperaemia, arthralgia and myalgia, lasting for a week or less and without any other aetiology. When reported cases meet the case definition, laboratory investigations are systematically conducted, including identification of dengue, chikungunya and Zika viruses.

Only for Martinique, from the emergence of the current Zika outbreak until late December 2015, samples were sent to the French NRC (IRBA Marseille) for laboratory confirmation. Starting from 4 January 2016, samples were also sent for biological analysis to the Laboratory of Virology at the University Hospital of Martinique. All laboratory results were collected by the Regional Office of the French Institute for Public Health Surveillance and entered into the infectious disease surveillance system. An extension of this system for Zika was developed in agreement with the French Data Protection Authority.

After confirmation of the first autochthonous case in a territory, the phase of active ZIKV circulation (phase 2) is declared and the enhanced surveillance continued, allowing vector control action around each identified case in order to contain the viral circulation.

Once the outbreak is declared (phase 3), i.e. once the weekly number of cases does not allow biological confirmation or vector control around each case, the aim of the surveillance is to monitor the epidemic course and document its severity to help the health authorities in their prevention and healthcare response. In phase 3, laboratory confirmation of all suspected cases is stopped. Instead, the surveillance of Zika syndrome is performed through weekly notification of clinical suspected cases by a voluntary sentinel network of GPs. This sentinel network represents more than 20% of GPs' total activity on each island, with a weekly response rate › 80%. The number of reported GP visits for Zika syndrome is extrapolated to total number of cases on the island using the ratio of all GPs to the participating sentinel GPs. Further, hospitals have to declare all admission for GBS and for other neurological disorders potentially related to ZIKV. An ad hoc surveillance system is in place to monitor and describe confirmed Zika cases in pregnant women as well as brain defects detected or suspected in fetuses or in newborns possibly linked to ZIKV infection.

Phase 4 is the ending of the outbreak and the time to determine the health burden and prepare feedback on the outbreak.

Table 1

Epidemiological situation and estimated number of Zika syndromes, confirmed cases of Guillain–Barré syndrome and Zika-positive pregnant women, by territory, as on 25 February 2016 (n = 9,077)

Territory	Week of identification of first confirmed case	Epidemiological phase	Suspected cases	Confirmed Zika cases with Guillain–Barré syndrome	Pregnant women confirmed Zika-positive
Guadeloupe	2016–02	2 - Viral circulation beginning	389	0	2
French Guiana	2015–51	3 - Outbreak	1,030	2 (0)	13
Martinique	2015–51	3 - Outbreak	7,600	4 (2)	31
Saint-Barthélemy	NA	1 - Pre emergence	0	0	0
Saint-Martin	2016–02	2 - Viral circulation beginning	58	0	1

NA: not applicable.

Furthermore, a scientific committee for surveillance of infectious and emerging diseases (Cemie) met regularly in order to assess the epidemiological situation and to raise recommendations regarding control measures.

Results

Epidemiological situation on 25 February 2016

Since the first report of ZIKV in the FTA, the number of confirmed or suspected cases has increased in a way that indicates continuous transmission of the virus in four affected territories. The epidemic phase, phase 3, has been declared on Martinique (20 January 2016) and French Guiana (22 January 2016), while Guadeloupe and Saint-Martin have remained in the phase 2 (active ZIKV circulation) (Table 1). By 25 February 2016, no ZIKV circulation had been detected on Saint Barthélemy.

On Martinique, the shape of the epidemic curve showed an important increase in the number of cases during the first five weeks of the outbreak (Figure 1A). All districts were affected by viral circulation and the estimated number of clinically suspected cases of Zika reported by GPs on Martinique was 7,600.

On French Guiana, the number of suspected cases increased more slowly (Figure 1B) and the outbreak spread in littoral areas (from St Laurent du Maroni to Cayenne). The cumulative estimated number of clinical suspected cases of Zika reported by GPs was 1,030.

On Guadeloupe, there were cases in most districts and the number of suspected cases reported by GPs increased steadily every week (Figure 1C). The cumulative estimated number of clinical suspected cases of Zika reported by GPs was 389 and the number of confirmed cases was 35.

On Saint Martin, the cumulative estimated number of clinical suspected cases of Zika reported by GPs was 58 and the number of confirmed cases was 11. No Zika case was laboratory-confirmed and no clinical suspected cases were reported on Saint-Barthélemy.

Four cases of GBS related to ZIKV infection were reported on Martinique and two on French Guiana. Two of the four cases on Martinique occurred in ZIKV-infected patients [9] and biological investigations are ongoing for the other cases. One hospital admission for neurological disorders potentially related to Zika was reported on Guadeloupe (Table 1). Thirty-one cases of ZIKV infection in pregnant women were reported on Martinique, 13 on French Guiana, two on Guadeloupe and one on Saint-Martin. No central nervous system malformations related to ZIKV infection were reported, no malformations in fetuses or infants and no deaths were identified as potentially linked to Zika.

Description of confirmed cases of Zika virus infection on Martinique from 24 November 2015 to 20 January 2016

Between 24 and November 2015, the day of symptom onset in the first case on Martinique, and 20 January 2016, 203 suspected cases of Zika infection were laboratory-confirmed by RT-PCR and/or seroneutralisation. Figure 2 shows their distribution by date of onset.

The male:female sex ratio was 0.43, with 61 men and 142 women. Among the 203 confirmed cases, ZIKV infection was confirmed for 11 pregnant women and for a hospitalised patient presenting GBS [9]. No death due to Zika infection was identified during the analysed period. The mean age of confirmed cases was 43 years with a standard deviation of ± 18 years (range: 4–89 years). Half of the confirmed cases were younger than 42 years.

Data from Martinique were compared with those from French Polynesia. The suspected case definition applied in French Polynesia was: maculopapular rash and/or fever and at least two of the following signs: conjunctival hyperaemia, arthralgia and/or myalgia or oedema of the hands/feet. The distribution of symptoms matching the case definition on Martinique vs French Polynesia is shown in Table 2.

Table 2

Frequency of case definition symptoms in confirmed Zika cases, Martinique (n = 203) and French Polynesia (n = 297), 24 November 2015–20 January 2016

Signs	Martinique (n = 203) n (%)	French Polynesia (n = 297) n (%)	Chi-squared test
Maculopapular rash	170 (84)	276 (93)	p = 0.001
Arthralgia	135 (67)	193 (65)	No difference
Fever	121 (60)	214 (72)	p < 0.05
Myalgia	121 (60)	131 (44)	p < 0.001
Conjunctival hyperaemia	68 (33)	187 (63)	p < 0.001

The most frequently reported symptoms were maculopapular rash (84%) and arthralgia (67%). Sixty percent of confirmed cases had fever and myalgia. Among the symptoms listed in the Zika case definition, the least frequently reported symptom was conjunctival hyperaemia (33%). Among the 33 confirmed cases without rash (16%), the reported clinical signs were arthralgia (n = 21), fever (n = 20) myalgia (n = 12) and conjunctival hyperaemia (n = 9).

Other clinical symptoms reported by cases but not included in the case definition are shown in Table 3 and included for example headaches (14%), pruritus (8%), gastrointestinal symptoms (8%), asthenia (5%), lymphadenopathy (5%), oedema (4%), retro-orbital pain (4%), ear, nose and throat symptoms (3%) and dizziness (1%).

Discussion

An epidemiological surveillance system for ZIKV infections was quickly implemented based on the previous experiences with dengue and chikungunya and has detected ZIKV circulation in the FTA. Monitoring data allowed us to follow the dynamics at the beginning of outbreak in the different territories. Nevertheless, owing to the large proportion of asymptomatic cases [10], the number of the estimated suspected cases (symptomatic cases) is likely to represent only the tip of the iceberg.

When comparing the clinical description of confirmed cases on Martinique to the ones on French Polynesia [11], we observed a statistically significant difference between the frequency of rash: 93% on French Polynesia and 84% on Martinique ($p < 0.001$). This clinical symptom was not mandatory in the case definition on French Polynesia but was more frequently reported than in Martinique. This difference can be due to the difficulty observing a rash on dark skin. The most important difference in reported symptoms was for conjunctival hyperaemia, with 63% of Polynesian confirmed cases vs 33% on Martinique ($p < 0.001$). Fever was also less frequent among ZIKV cases on Martinique than on French Polynesia, with respectively 60% and 72% ($p < 0.05$). Conjunctival hyperaemia and myalgia were not dependent on the case definition. This study of laboratory-confirmed cases selected through a case definition did not allow testing the specificity and sensitivity of our case definition. However, our results show that the rash, foundation of our case definition, may be absent in a considerable proportion of patients.

These results are of importance for the implementation of a suspected case definition, the main tool for epidemiological surveillance systems, in territories where ZIKV infection is currently spreading. The case definition adopted on Martinique is maintained for outbreak surveillance by GPs as it has a suitable positive predictive value. Furthermore, widening of the case definition criteria could be considered so as to be more sensitive in specific situations such as the diagnosis of Zika in pregnant women for a reactive intervention.

The epidemiological situation in the FTA is a concern for European areas where *Aedes albopictus* is established [12]. To adapt prevention messages and improve knowledge, it is essential to continue the global surveillance with particular attention to complications (neurological cases [13]), pregnant women and children born from infected mothers [14].

At this stage of the introduction of ZIKV on the South American mainland, the laboratory of the NRC in French Guiana who first sequenced the ZIKV genome circulating in America [15] do not see a marked spatiotemporal phylogeny (Asian lineage in the Americas), nor a specific cluster. Given the low genetic variability observed (in 10,000 bp), using a Bayesian maximum clade credibility model did not seem suitable.

Current situation

As on 7 July 2016, the epidemic phase (phase 3) has been declared on Guadeloupe (28 April 2016) and Saint-Martin (15 June 2016); ZIKV circulation has been detected on Saint-Barthélemy and 185 clinical suspected cases have been estimated.

The cumulative estimated number of clinical suspected Zika cases reported by GPs since the beginning of outbreak is 32,400 on Martinique, 20,070 on Guadeloupe, 8,715 on French Guiana and 1,260 on Saint-Martin. Twenty-one cases of GBS related to ZIKV infection have been reported on Martinique, four on French Guiana and four on Guadeloupe. In addition, biological

Table 3

Other clinical signs in confirmed Zika cases, Martinique, 24 November 2015–20 January 2016 (n = 203)

Signs	Number of cases	Frequency
Headaches	28	14%
Itch	17	8%
Gastrointestinal signs	16	8%
Asthenia	10	5%
Lymphadenopathy	10	5%
Oedema	8	4%
Retro-orbital pain	8	4%
Ear, nose and throat signs	6	3%
Dizziness	3	1%

investigations are ongoing for sixteen further GBS cases. A total of 744 cases of ZIKV infection in pregnant women have been reported on French Guiana, 384 on Martinique, 225 on Guadeloupe and 12 on Saint-Martin. Nine malformations in fetuses or infants related to ZIKV infection have been reported or suspected to be in FTA. Finally, one death has been identified as potentially linked to Zika on Martinique [16].

Zika Surveillance Working Group

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Conflict of interest

None declared.

Authors' contributions

EDV, ML and AC wrote the manuscript. Staff of the Regional Office of French Public Health Agency and the Zika Surveillance Working Group took part in alert and surveillance systems of Zika. FN, RC, ILG, MM, OF, DR, SM, CH and PHA collaborated in molecular biology and serological techniques. All authors participated in the Zika surveillance. All authors read and approved the final manuscript.

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Outbreak of pulmonary *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* infections related to contaminated bronchoscope suction valves, Lyon, France, 2014

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In April 2014, pulmonary *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* co-infections potentially related to bronchoscopic procedures were identified in the intensive care units of a university hospital in Lyon, France. A retrospective cohort of 157 patients exposed to bronchoscopes from 1 December 2013 to 17 June 2014 was analysed. Environmental samples of suspected endoscopes were cultured. Bronchoscope disinfection was reviewed. Ten cases of pulmonary *P. aeruginosa*/*S. maltophilia* co-infections were identified, including two patients with secondary pneumonia. Eight cases were linked to bronchoscope A1 and two to bronchoscope A2. Cultures deriving from suction valves were positive for *P. aeruginosa*/*S. maltophilia*. Exposure to bronchoscopes A1 and A2 was independently coupled with increased risk of co-infection (adjusted odds ratio (aOR) = 84.6; 95% confidence interval (CI): 9.3–771.6 and aOR = 11.8, 95% CI: 1.2–121.3). Isolates from suction valves and clinical samples presented identical pulsotypes. The audit detected deficiencies in endoscope disinfection. No further cases occurred after discontinuation of the implicated bronchoscopes and change in cleaning procedures. This outbreak of pulmonary *P. aeruginosa*/*S. maltophilia* co-infections was caused by suction valve contamination of two bronchoscopes of the same manufacturer. Our findings underscore the need to test suction valves, in addition to bronchoscope channels, for routine detection of bacteria.

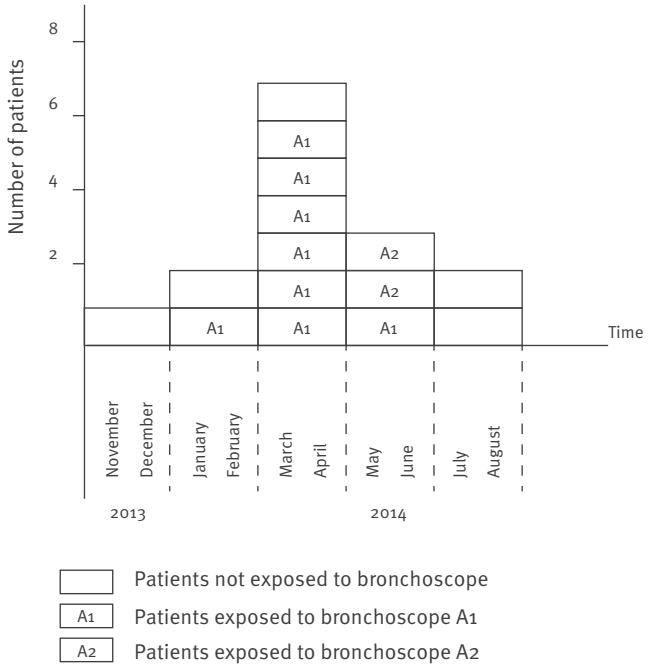
Introduction

Outbreaks and pseudo-outbreaks associated with bronchoscopic procedures have been reported in the literature [1-3]. The microorganisms most commonly implicated in these outbreaks are *Pseudomonas aeruginosa* [4-8], *Mycobacterium tuberculosis* [9,10], and *M. chelonae* [11,12]. In most cases, only a single microorganism is identified, infection by several microorganisms is less frequent [13,14]. Contamination in past outbreaks had various causes, including water from automated endoscope reprocessors [11,15], damaged [7] or defect bronchoscopes [6,13,16], misuse of connectors, deficiencies in the cleaning process and, much less frequently, contamination of suction valves [17,18]. To reduce the risk of nosocomial infections from bronchoscopic procedures, national bronchoscopy guidelines have been established in several countries, including France [19-24]. Despite the increasing experience of bronchoscopic teams, up-to-date guidelines and outbreak reports, patients might still be exposed to contaminated bronchoscopes.

In April 2014, we were alerted to two cases of early-onset pneumonia with *P. aeruginosa* and *Stenotrophomonas maltophilia* in young and immunocompetent trauma patients, after exposure to the same bronchoscope in Edouard Herriot Hospital (Hospices Civils de Lyon, Lyon, France). Here, we report the results of this outbreak investigation and the impact of control measures.

Figure 1

Epidemic curve of *Pseudomonas aeruginosa*- and *Stenotrophomonas maltophilia*-positive cultures isolated from respiratory samples of patients exposed or not exposed to bronchoscopes, France, November 2013–August 2014 (n=15)



Methods

Setting

Edouard Herriot Hospital is a 900-bed university-affiliated hospital from Hospices Civils de Lyon in Lyon, France, with four intensive care units (ICUs) accounting for 62 beds overall (ICUs #A, #B, #C and #D). Each year, more than 350 bronchoscopic and 2,000 cleaning procedures are performed in the hospital. In 2014, eight bronchoscopes were used in the endoscopy suite: three of the same model from manufacturer A (bronchoscopes A2, A2, A3) and five from manufacturer B (bronchoscopes B1, B2, B3, B4, B5). These bronchoscopes were deployed in ICUs, operating rooms or other care units.

Bronchoscope cleaning procedures

Bronchoscope cleaning and storage are centralised in ICU #C. Immediately after use, external bronchoscope surfaces are wiped with compresses and channels flushed with water. The bronchoscopes are taken to ICU #C for cleaning, as soon as possible, by authorised personnel, in accordance with a standardised local protocol adapted from French national recommendations [22]. A tightness test is performed before the bronchoscopes are soaked in detergent-disinfectant (Phagoclean NH4, Laboratoire Phagogène, Christeyns, France) and cleaned manually by wiping the outer surface, brushing and flushing internal channels. Each removable component is removed and cleaned. After rinsing, the bronchoscopes are processed in an automated endoscope reprocessor (Soluscope Series 3 PA, Soluscope, Aubagne, France) with disinfectant (Soluscope P), additive (Soluscope A) and detergent (Soluscope C+). Finally, after drying, the bronchoscopes are kept in an aseptic storage cabinet (Medi 72, Medinorme, La Seyne-sur-Mer, France). Standardised forms are completed for each procedure to maintain traceability.

Outbreak investigations

In April 2014, two cases of early-onset pneumonia with *P. aeruginosa/S. maltophilia* in young, not immunocompromised trauma patients in ICU #C were reported to the Infection Control Unit. These patients were exposed to the same bronchoscope (A1). An investigation was launched. In June 2014, two further pulmonary *P. aeruginosa/S. maltophilia* co-infections in patients exposed to bronchoscope A2 were encountered in ICU #B. An additional investigation was conducted with a retrospective cohort of patients exposed to bronchoscopes from 1 December 2013 to 17 June 2014 in Edouard Herriot Hospital and a nested case–control study.

Cases were defined as patients exposed to bronchoscopes between 1 December 2013 and 17 June 2014, with *P. aeruginosa/S. maltophilia*-positive cultures isolated from clinical respiratory samples. We included only positive cultures from broncho-alveolar lavage, tracheobronchial aspiration or plugged telescoping catheter (Combicath), obtained during or after the bronchoscopic procedure. Sputum samples were not considered. Controls were defined as patients exposed to bronchoscopes in the same period but without positive respiratory sample cultures of the microorganisms found on bronchoscopes, namely *P. aeruginosa, S. maltophilia, Klebsiella pneumoniae, Enterobacter cloacae* or *Achromobacter xylosoxidans*. For the epidemic curve, the period of interest began on 1 November 2013.

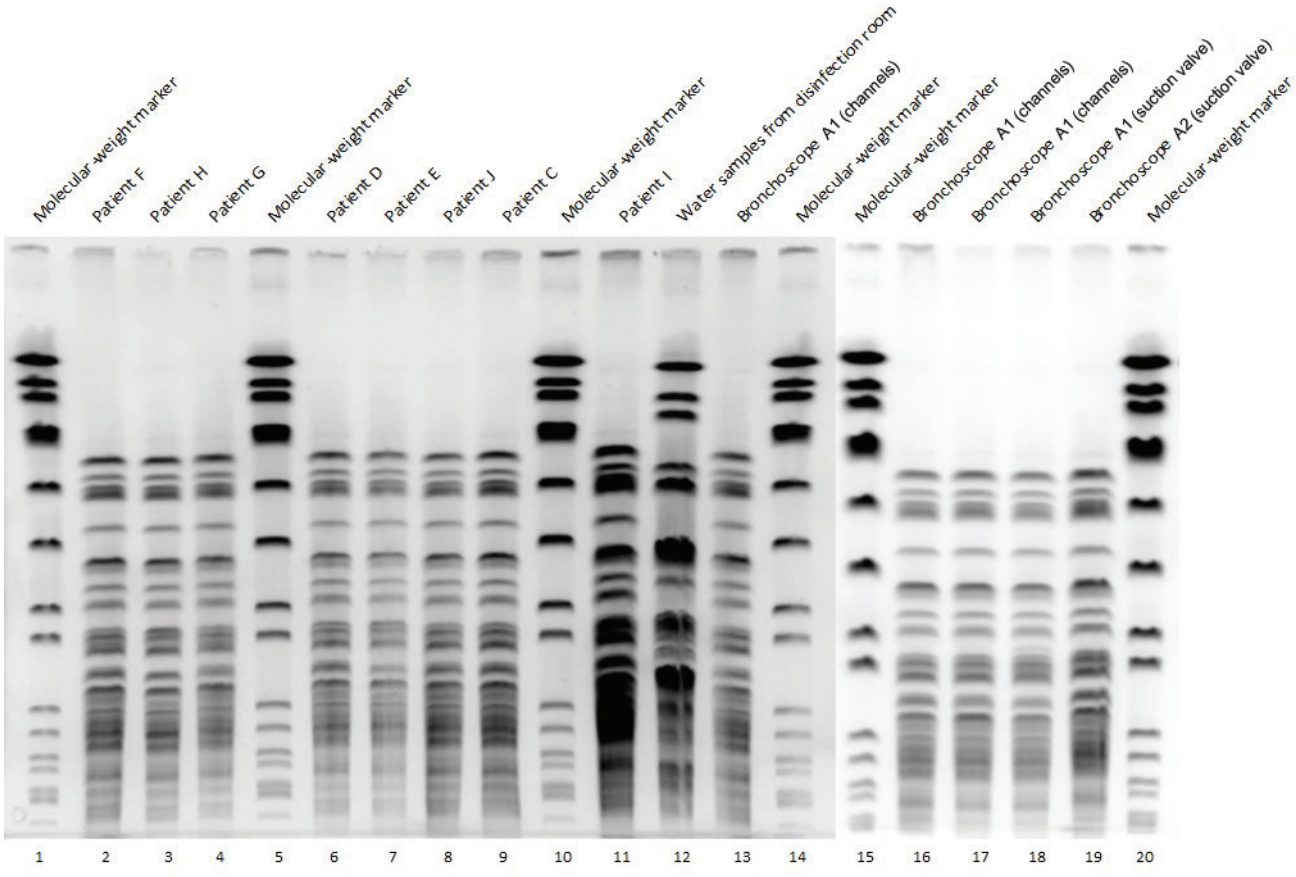
Patients exposed to bronchoscopes were identified from standardised, prospectively collected forms detailing bronchoscope use. Clinical sample results were obtained from the microbiological laboratory (according to European guidelines [25]) for patients exposed to bronchoscope for whom a microbiological sample was available, and medical case records were reviewed. Bronchoscope cleaning processes were audited by the Infection Control Unit. Prospective surveillance was implemented starting from the first investigation, as soon as the infection control team was informed. Every day, a member of the infection control unit was looking for new cases, checking results of cultures isolated from respiratory samples from patients in Edouard Herriot Hospital.

Environmental investigation

According to French guidelines [24], samples from suspected bronchoscope channels were taken by two authorised personnel, after cleaning and at least six

Figure 2

Pulsed-field gel electrophoresis of *Pseudomonas aeruginosa* isolates from clinical (n = 8) and environmental (n = 6) samples, France, November 2013–August 2014



Macrorestriction profiles of total DNA from clinical and environmental isolates were acquired by pulsed-field gel electrophoresis (PFGE) on a CHEF-DR III unit (Bio-Rad, Hercules, US). Isolates of *P. aeruginosa* from clinical samples (patients C, D, E, F, G, H, I and J) were identical to isolates from channels and suction valve of bronchoscope A1 and to isolates from the suction valve of bronchoscope A2, but differed from tap water isolates from the disinfection room. *Staphylococcus aureus* NCTC 8325 (with *Sma*I as restriction enzyme) was used as a reference (molecular weight marker), and PFGE patterns were analysed visually.

hours of storage. Sixty mL of Pharmacopeia dilution solution with antimicrobial inactivators (DNP buffer, AES Chemunex, bioMérieux, Marcy l'Etoile, France) were flushed into proximal ports and collected in sterile cups at the distal end of the operating channel. As the first set of cultures from bronchoscope channel samples were negative, bronchoscope suction valves and biopsy valves from suspected bronchoscopes were sampled.

In addition, surface samples from the aseptic storage cabinet for bronchoscopes, water samples from automated endoscope reprocessors and tap water samples from ICU #C were cultured.

Molecular typing

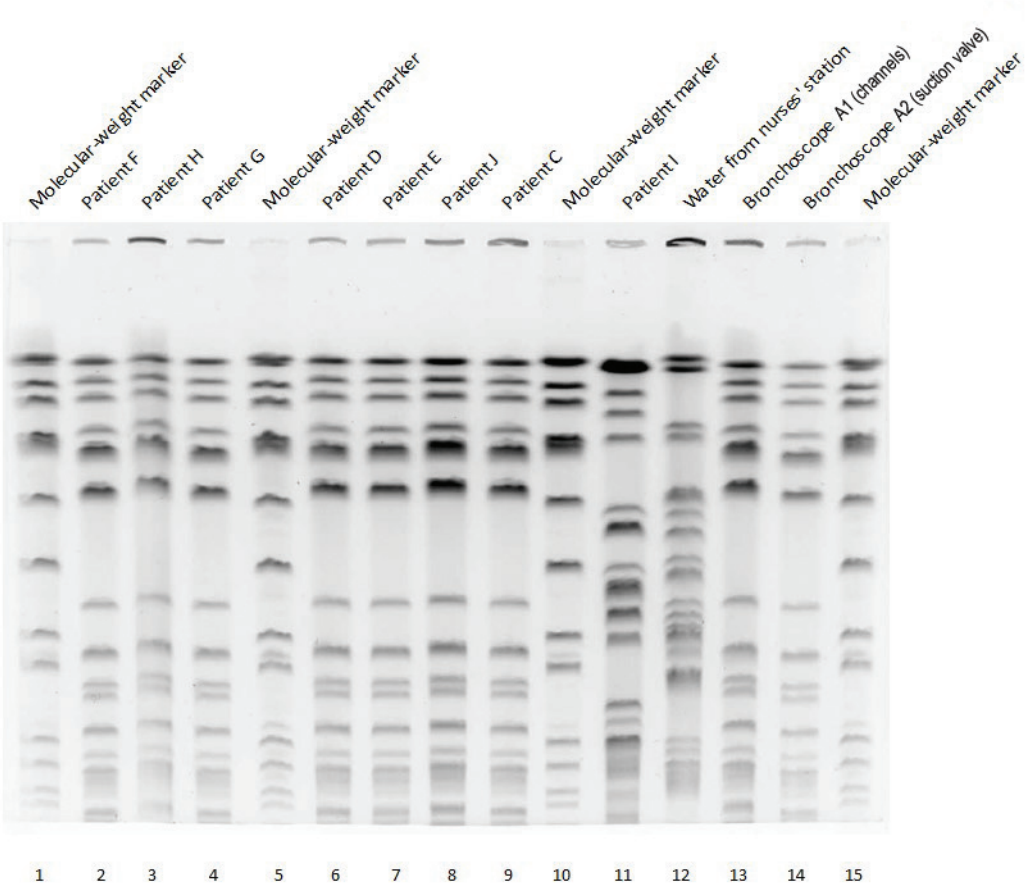
Macrorestriction profiles of total DNA from clinical and environmental isolates were acquired by pulsed-field gel electrophoresis (PFGE) on a CHEF-DR III unit (Bio-Rad, Hercules, United States (US)) [26]. *Dra*I and *Xba*I served as restriction enzymes for *P. aeruginosa* and *S. maltophilia*, respectively. We ensured that the gels were comparable by including *Staphylococcus aureus* NCTC 8325 (with *Sma*I as restriction enzyme) as a reference, and PFGE patterns were analysed visually.

Statistical analysis

In the nested case–control study, all exposures to bronchoscopes were considered to be potential risks. Other potential risk factors were unit, patient age, sex and number of bronchoscopic procedures per patient. To identify characteristics linked with the risk of being a case, categorical variables were compared by chi-square test, and continuous variables by the Mann-Whitney U test. All tests were two-tailed. A p value of ‹0.05 was considered significant. Univariate and multivariate logistic regression was undertaken with Stata 11.0 software (StataCorp, College Station, US).

Figure 3

Pulsed-field gel electrophoresis of *Stenotrophomonas maltophilia* isolates from (n = 8) and environmental (n = 3) samples, France, November 2013–August 2014



Macrorestriction profiles of total DNA from clinical and environmental isolates were acquired by pulsed-field gel electrophoresis (PFGE) on a CHEF-DR III unit (Bio-Rad, Hercules, US). Isolates of *S. maltophilia* isolates from clinical samples (except for patient I) were identical to isolates from the suction valve of bronchoscope A2 and to isolates from the channels of bronchoscope A1, but differed from tap water isolates found in the nurses' station. *Staphylococcus aureus* NCTC 8325 (with *Sma*I as restriction enzyme) was used as a reference (molecular weight marker), and PFGE patterns were analysed visually.

Results

Between 1 December 2013 and 17 June 2014, 157 patients were exposed to at least one bronchoscope, and 216 bronchoscopic procedures were undertaken. Median age was 62 years (interquartile range (IQR): 49–73 years), and 111 patients (71%) were male. Overall, 10 patients had *P. aeruginosa/S. maltophilia*-positive cultures isolated from respiratory sampling; 35 patients had at least one respiratory sample with *P. aeruginosa*, *S. maltophilia*, *K. pneumonia*, *E. cloacae or A. xylosoxidans,* but did not fulfil the criteria of the case definition, and the respiratory samples of 112 patients were negative for all of these pathogens. The 10 cases identified were all men, with a median age of 52 years (IQR: 23–67 years) (Table 1), three were previously hospitalised and nine were intubated during their ICU stay. Among them, two patients had secondary pneumonia, nine and 11 days after bronchoscopy. Three cases died during ICU stay and their deaths were not related to bronchoscope contamination. Eight cases were associated with bronchoscope A1 and two cases with bronchoscope A2. During the outbreak, the attack rate among cases exposed to bronchoscopes was 9.4% between February and June 2014 compared with 0% between December 2013 and January 2014 ($p<0.05$); five patients had *P. aeruginosa/S. maltophilia* positive respiratory samples but had not been exposed to a bronchoscope (Figure 1).

We compared exposed patients co-infected with *P. aeruginosa* and *S. maltophilia* (n = 10) to non-infected patients (n = 112) during the outbreak period (Table 2). Univariate analysis disclosed that exposure to bronchoscope A1 or A2, hospitalisation unit and number of bronchoscopic procedures per patient were associated with increased risk of being a case. After multivariate

Table 1

Demographic and clinical characteristics of patients with pulmonary *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* co-infection exposed to bronchoscopes, France, November 2013–August 2014 (n=10)

Patient	A	B	C	D	E	F	G	H	I	J
Age group (years)	40-49[a]	70-79	50-59	30-39	18-29	18-29	50-59	18-29	60-69	70-79
ICU	ICU #A	ICU #B	ICU #A	ICU #C	ICU #C	ICU #C	ICU #A	ICU #C	ICU #B	ICU #B
Cause of hospital admission	Pneumonia	Respiratory distress syndrome, coma	Fever and aplasia after autologous transplantation	Abdominal wound	Polytrauma	Polytrauma, coma	Septic shock, pneumonia, waiting for lung transplant	Polytrauma	Cardiac arrest	Multiple organ failure (post-operative)
Immunosuppression	No	No	Yes	No	No	No	Yes	No	No	Yes
Death (cause of death)	No	Yes[b]	Yes[b]	No	No	No	Yes[b]	No	No	No
Time between hospitalisation and bronchoscopic procedure (days)	6	0	3	3	3	1	0	9	10	7
Bronchoscope exposure	A1	A1	A1	A1	A1	A1	A1	A1	A2	A2
Microbiology results	*P. aeruginosa*, *S. maltophilia*	*P. aeruginosa*, *S. maltophilia*, *E. coli*, *C. tropicalis*	*P. aeruginosa*, *S. maltophilia*, *influenza A virus*	*P. aeruginosa*, *S. maltophilia*	*P. aeruginosa*, *S. maltophilia*, *S. aureus*	*P. aeruginosa*, *S. maltophilia*, *S. aureus*	*P. aeruginosa*, *S. maltophilia*, *E. cloacae*, *K. pneumoniae*	*P. aeruginosa*, *S. maltophilia*, *K. pneumoniae*, *C. albicans*	*P. aeruginosa*, *S. maltophilia*	*P. aeruginosa*, *S. maltophilia*, *A. xylosoxidans*
Secondary pneumonia	No	Yes	No	No	No	Yes	No	No	No	No

ICU: intensive care unit; M: male; A1: bronchoscope A1; A2: bronchoscope A2.

[a] To anonymise the description of cases, the age is reported by stratum.

[b] Unrelated to bronchoscopic procedure.

Table 2

Factors associated with the risk of *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* co-infection, France, November 2013–August 2014 (n=122)

Characteristics	*Pa/Sm* co-infection n (%)	Non-infected[a] n (%)	p	Crude odds ratio (95% CI)
Total	10	112		
Age (years)	52 (23-67)[b]	62 (49-72)[b]	0.07	0.96 (0.92–1.0)[b,c]
Sex (female)	0 (0)	39 (35)	0.02	NE
Bronchoscope exposure[d]				
Bronchoscope A1	8 (80)	9 (8)	<0.001	45.8 (8.4–248.7)[e]
Bronchoscope A2	4 (40)	16 (14)	0.03	4.0 (1.02–15.8)[e]
Bronchoscope A3	2 (20)	17 (15)	0.69	1.4 (0.3–7.2)[e]
Bronchoscope B1	0 (0)	0 (0)	NA	NE
Bronchoscope B2	1 (10)	24 (21)	0.39	0.4 (0.05–3.4)[e]
Bronchoscope B3	2 (20)	25 (22)	0.86	0.9 (0.2–4.4)[e]
Bronchoscope B4	0 (0)	27 (24)	0.08	NE
Bronchoscope B5	0 (0)	13 (12)	0.25	NE
Unit				
Intensive care unit	10 (100)	70 (62)	0.02	NE
Operating rooms	0 (0)	30 (27)	0.06	NE
Other units	0 (0)	12 (11)	0.28	NE
Number of bronchoscopic procedures				
1	5 (50)	95 (85)	0.006	1.0 (reference)
≥ 2	5 (50)	17 (15)		5.6 (1.5–21.4)

NA: not applicable; NE: could not be estimated; *Pa/Sm*: *Pseudomonas aeruginosa/Stenotrophomonas maltophilia*.

[a] Patients for whom *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Klebsiella pneumonia, Enterobacter cloacae* or *Achromobacter xylosoxidans* could not be isolated from respiratory samples.

[b] Median interquartile range.

[c] For one year older.

[d] More than one exposure was possible.

[e] Compared with the absence of exposure to this particular endoscope.

analysis, exposure to bronchoscope A1 and bronchoscope A2 was independently associated with heightened risk of *P. aeruginosa/S. maltophilia* co-infection (adjusted odds ratio (aOR) = 84.6, 95% confidence interval (CI): 9.3–771.6 and aOR = 11.8, 95% CI: 1.2–121.3, respectively). No further cases occurred after sequestration of the two implicated bronchoscopes.

Endoscopic and environmental cultures

As soon as the first two cases with *P. aeruginosa/S. maltophilia* in patients exposed to bronchoscope A1 were reported, the device was investigated and taken out of service. However, as bronchoscope channel samples were negative in bacteriological testing, we allowed it to be used again. Meanwhile, ICU #C tap water was sampled. *P. aeruginosa* grew from one sample in the disinfection room, and *S. maltophilia* grew from one sample in the nurses' station. Contaminated washbasins were disinfected, and control samples were negative. Thus, contaminated tap water was deemed to be the potential source of infection. At that time, the source of contamination was considered to be controlled, and active surveillance was implemented.

However, in May 2014, another case of *P. aeruginosa/S. maltophilia* pneumonia attributed to bronchoscope A1 was detected. Bronchoscope A1 was withdrawn from circulation and sent to the manufacturer for technical expertise. Bronchoscope channels and valves were sampled by the infection control team. Channel samples grew both *P. aeruginosa and S. maltophilia,* and the suction valve grew *Burkholderia cepacia, E. cloacae, K. pneumonia* and *P. aeruginosa*. The biopsy valve culture remained negative. The expert report noted that the suction valve had a porous seal. The environmental investigation was extended to the aseptic storage cabinet and water from automated endoscope reprocessors, but these sample cultures were negative.

In June 2014, two additional *P. aeruginosa/S. maltophilia* pneumonia cases were reported in patients exposed to bronchoscope A2 in ICU #B; it was removed from use. Channel and biopsy valve samples were negative, but the suction valve grew *P. aeruginosa* and *S. maltophilia*. Sampling was extended to bronchoscope A3, but channel and valve cultures were negative. Routine samples from the endoscopes of other

brands were all negative for *P. aeruginosa or S. maltophilia* during the outbreak period.

Molecular typing

PFGE revealed that isolates of *P. aeruginosa* (Figures 2 and 3) from clinical samples (patients C, D, E, F, G, H, I and J) were identical to isolates from channels and suction valve of bronchoscope A1 and to isolates from the suction valve of bronchoscope A2, but differed from isolates obtained from tap water in the disinfection room. Similarly, *S. maltophilia* isolates from clinical samples (except for patient I) were identical to isolates from the suction valve of bronchoscope A2 and to isolates from the channels of bronchoscope A1, but differed from tap water isolates found in the nurses' station. Clinical isolates from patients A and B could not be recovered for typing.

Bronchoscope cleaning processes

Bronchoscope cleaning processes were audited by the Infection Control Unit with a standardised form. Some deficiencies were detected such as delays between endoscopy and cleaning. Moreover, the tightness test was not always performed before manual cleaning. However, these deficiencies were not specific to bronchoscopes from manufacturer A. Corrective actions were taken. Protocols were updated, traceability was improved, and single-use bronchoscopes were provided during the night and on-call duties in order to avoid latency between bronchoscopy and cleaning. As of 24 June 2016, no contamination of bronchosocope with *P. aeruginosa/S. maltophilia* has been identified, no new case related to bronchoscope exposure has occurred since bronchoscope disinfection was improved.

Discussion

From December 2013 to June 2014, an outbreak of *P. aeruginosa/S. maltophilia* co-infections was investigated in 10 patients undergoing bronchoscopy. These cases were related to two bronchoscopes of the same model from which *P. aeruginosa/S. maltophilia* were isolated from the suction valves. Clinical and contaminated bronchoscope isolates showed similar PFGE patterns. Two secondary pneumonia infections were identified among the cases. The respiratory samples may have been contaminated in the eight other cases, but antibiotic therapy was initiated for all patients and may have prevented the development of nosocomial pneumonia.

One of the key issues is to know how bronchoscope A1 was contaminated. As environmental sources of contamination were excluded, it may have been tainted during a bronchoscopic procedure on a patient colonised or infected by *P. aeruginosa/S. maltophilia*. Persistent contamination was probably partially due to defective bronchoscope cleaning as some deficiencies were highlighted by the audit. Furthermore, the complexity of suction valve cleaning and disinfection compared to other bronchoscopes might have contributed to the event.

Detection of this outbreak may have been further delayed because there was no specific surveillance of patients exposed to bronchoscopes. Moreover, the source of contamination was found by extended bronchoscope sampling. Bronchoscope disinfection is routinely assessed by channel sampling, as recommended in French guidelines [24]. The first results of bronchoscope contamination detection were probably false negatives. This outbreak highlights the benefits of routinely testing suction valves to look for bacterial contamination of bronchoscopes. In case of suspected contamination, suction valves should be systematically tested. If contaminated, they should be removed and replaced or sterilised. This outbreak raises questions about the cleaning process for suction valves. Indeed, there is no consensus on whether single-use suction valves, high-level suction valve disinfection or sterilisation after manual cleaning should be preferred. The manufacturer confirmed the lack of recommendations for suction valve management. The expert report stated that the submitted suction valve had porous seals which increased the risk of contamination. Preventive replacement of suction valves should be considered.

Faced with the contamination of two bronchoscopes of the same model, within the same part (suction valves), we wonder about increased risks posed by these devices. We therefore reported the event to the French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du médicament et des produits de santé (ANSM)), where no other notifications concerning these bronchoscopes were filed. Disparities in the hospital's stock of bronchoscopes regarding brands or preventive maintenance and lack of preventive maintenance were probable contributing factors. The two bronchoscopes under investigation were bought in 2007 and 2008 and did not have preventive maintenance contracts with the manufacturer.

Other outbreaks or pseudo-outbreaks tied to suction valve contamination have been described, mostly before the 2000s, but they involved mycobacteriae [17,18]. Bronchoscope contamination by *P. aeruginosa/S. maltophilia* was reported in the investigation of a pseudo-outbreak in Baltimore, US in 2008 [27] and more recently, contamination by *S. maltophilia* was reported in the Netherlands [28].

Our investigations had some limitations. We did not find the index case, and the route of pathogen transmission from bronchoscopes A1 and A2 was not clearly identified. Transmission may have occurred through one secondary case exposed to both bronchoscopes, or perhaps through the connectors. Moreover, *B. cepacia, E. cloacae* and *K. pneumonia* were identified on one bronchoscope suction valve. Our case definition did not include patients with respiratory samples positive

for these microorganisms. We may have underestimated the magnitude of the outbreak.

Conclusion

We investigated an outbreak of *P. aeruginosa/S. maltophilia* pulmonary infections caused by suction valve contamination of two bronchoscopes from the same manufacturer. While bronchoscope contamination might be attributed to deficiencies in bronchoscope cleaning processes, suction valves of these bronchoscopes have a particular design which may increase the risk of contamination; the manufacturer was informed in the process and they were cooperative. No further confirmed cases exposed to bronchoscope have been detected as at 24 June 2016. Our findings underscore the need to test not only bronchoscope channels but also suction valves regularly for routine detection of bacteria. The large number of patients worldwide who are exposed daily to bronchoscope examinations highlights the necessity for regular updates of guidelines, appropriate hygiene procedures and reporting new risks to improve patient safety.

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Conflict of interest

None declared.

Authors' contributions

Marine Guy: performed epidemiological investigations, analysis, manuscript writing. Philippe Vanhems: project leader, performed epidemiological investigations, reviewed the manuscript. Cédric Dananché: performed epidemiological investigations, reviewed the manuscript. Pierre Cassier: performed environmental microbiologic analysis, reviewed the manuscript. Anne Regard: performed epidemiological investigations, reviewed the manuscript. Monique Hulin: performed epidemiological investigations, reviewed the manuscript

Olivier Dauwalder: performed microbiologic analysis, reviewed the manuscript. Xavier Bertrand: performed pulsed-field gel electrophoresis analysis, reviewed the manuscript. Jullien Crozon-Clauzel: participated in epidemiological investigation, reviewed the manuscript. Bernard Floccard: participated in epidemiological investigation, reviewed the manuscript. Laurent Argaud: participated in epidemiological investigation, reviewed the manuscript. Michel Perraud: performed epidemiological investigations, reviewed the manuscript. Thomas Bénet: project leader, performed epidemiological investigations, analysis and interpretation of results, manuscript writing.

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Research article

The epidemiology and transmissibility of Zika virus in Girardot and San Andres island, Colombia, September 2015 to January 2016

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Transmission of Zika virus (ZIKV) was first detected in Colombia in September 2015. As of April 2016, Colombia had reported over 65,000 cases of Zika virus disease (ZVD). We analysed daily surveillance data of ZVD cases reported to the health authorities of San Andres and Girardot, Colombia, between September 2015 and January 2016. ZVD was laboratory-confirmed by reverse transcription-polymerase chain reaction (RT-PCR) in the serum of acute cases within five days of symptom onset. We use daily incidence data to estimate the basic reproductive number (R_0) in each population. We identified 928 and 1,936 reported ZVD cases from San Andres and Girardot, respectively. The overall attack rate for reported ZVD was 12.13 cases per 1,000 residents of San Andres and 18.43 cases per 1,000 residents of Girardot. Attack rates were significantly higher in females in both municipalities ($p < 0.001$). Cases occurred in all age groups with highest rates in 20 to 49 year-olds. The estimated R_0 for the Zika outbreak was 1.41 (95% confidence interval (CI): 1.15–1.74) in San Andres and 4.61 (95% CI: 4.11–5.16) in Girardot. Transmission of ZIKV is ongoing in the Americas. The estimated R_0 from Colombia supports the observed rapid spread.

Introduction

First isolated in the Zika Forest of Uganda in 1947, Zika virus (ZIKV) is a flavivirus of the same genus as dengue virus and yellow fever virus. It is an arbovirus primarily transmitted by *Aedes aegypti* mosquitoes [1]. Although ZIKV has circulated in Africa and Asia since the 1950s, little is known about its transmission dynamics [2]. Recent outbreaks in Yap Island in Micronesia (2007), French Polynesia (2013), and other Pacific islands, including Cook Islands, Easter Island, and New Caledonia (2014), indicate that ZIKV has spread beyond its former geographical range [3-6]. In April 2015 ZIKV was isolated in the north-east of Brazil [7].

As of June 2016, around 500,000 Zika virus disease (ZVD) cases have been estimated in Brazil, and autochthonous circulation has been observed in 40 countries in the Americas. Further spread to countries within the geographical range of *Ae. aegypti* mosquitoes is considered likely [8].

Infection with ZIKV typically causes a self-limited dengue-like illness characterised by arthralgia, conjunctivitis, exanthema and low-grade fever [9]. While illness is believed to be mild or asymptomatic in ca 80% of the infections [10], an increase in rates of Guillain–Barré syndrome (GBS) has been observed during ZIKV outbreaks [8,11,12]. Furthermore, in October 2015, the Brazilian Ministry of Health reported a dramatic increase in cases of microcephaly in north-east Brazil where ZIKV had been circulating [13].

On the basis of the possible link between ZIKV, GBS and microcephaly, the World Health Organization (WHO) declared a public health emergency on 1 February 2016 [14,15].

In Colombia, the virus was first detected in mid-September 2015 in a municipality called Turbaco on the Caribbean coast. Turbaco is located 10.1 km from

Figure 1

Location of the two Zika virus outbreak settings investigated, Colombia, September 2015–January 2016

Colombia figures in yellow on the map, with a dark square for the capital city Bogotá. The two settings of Zika virus disease outbreaks investigated in this study are indicated by a star. On the map, the city of Cartagena is also shown, because in Colombia, Zika virus was first detected ca 10 km from this city, before spreading to other locations in the country.

Cartagena (ca 20 min drive), a well-known commercial and tourism hub (Figure 1).

In October 2015, ZIKV spread through the central region of the country, appearing in areas infested with *Ae. aegypti* and with endemic dengue transmission and ongoing circulation of chikungunya virus (CHIKV) since 2014. By April 2016, Colombia had reported over 65,000 cases of ZVD, making it the second country most affected by ZIKV after Brazil [16,17]. Up to April 2016, 280 cases of neurological complications including GBS as well as seven deaths possibly associated with ZVD had been reported in Colombia [18]. As of April 2016, there have been four confirmed cases of ZIKV congenital syndrome in the country [17].

In this paper we describe local ZIKV outbreaks between September 2015 and January 2016 in Girardot and San Andres island, two different geographical areas in Colombia for which detailed epidemiological data are available. We conduct an investigation to define the epidemiological features of these outbreaks and to estimate the corresponding transmission parameters.

Methods

Settings

San Andres

San Andres is the largest island in a Colombian archipelago in the Caribbean Sea located ca 750 km north of mainland Colombia and 230 km east of Nicaragua (Figure 1). The island has an area of 27 km2, a population of 54,513 inhabitants across 13,652 households, and a population density of 2,932 habitants per km2 in 2010 [19,20]. Tourism is the most important economic activity in San Andres, with two high touristic seasons: June to July and December to January. The average temperature is 27.3 °C, and 80% of the total annual rainfall of 1,700 mm occurs during the heavy rainy season between October and December. The weather is humid subtropical with occasional hurricanes. The population in San Andres has two main ethnic groups: Afro-Colombians (17.5%) and Raizal (an ethnic group of mixed Afro-Caribbean and British descent) (39.2%) [20]. The most productive breeding sites of *Ae. aegypti* in San Andres are unprotected water containers located in the households. San Andres has experienced low dengue transmission (annual incidence rates ‹1%) since 1983. Since 1995, the frequency of dengue outbreaks increased every two to five years with a mean annual incidence of 0.43 cases per 1,000 inhabitants between 1999 and 2010 [19]. In 2014, CHIKV began circulating in San Andres, and that year it reached an annual incidence of 3.65 cases per 1,000 inhabitants [21].

Girardot

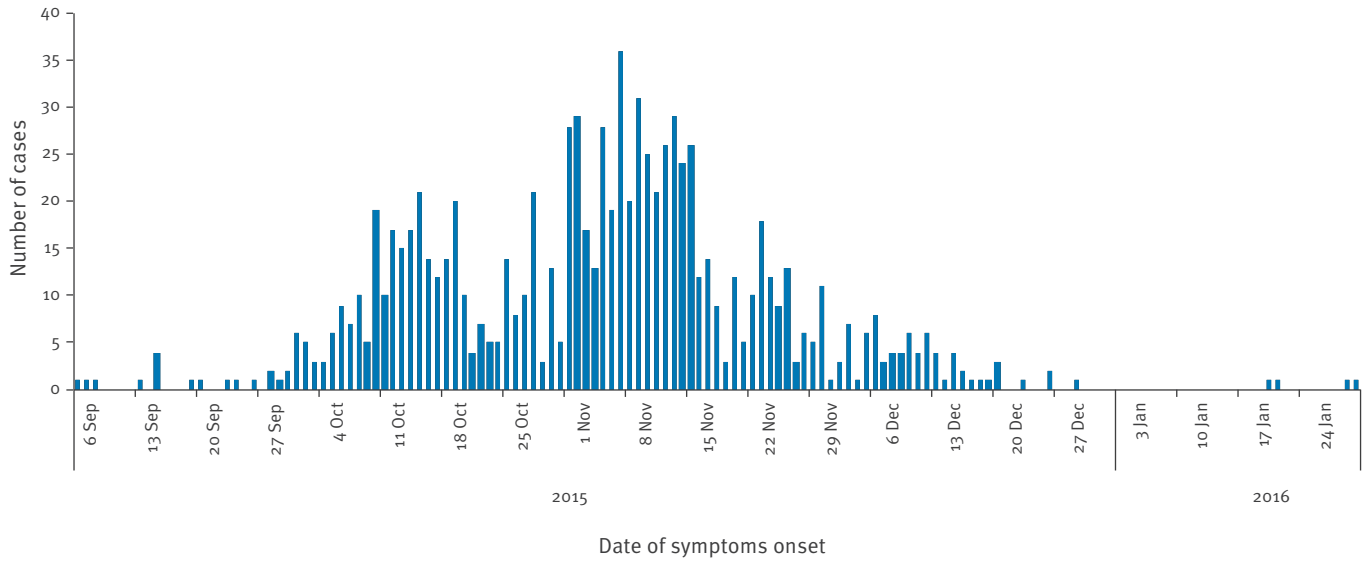
Girardot is a very central and well-connected municipality in continental Colombia. It is located 134 km (2 hours' drive) from the capital city of Bogota, and it is a popular tourist destination for residents of Bogota (Figure 1). Girardot has 102,225 inhabitants across ca 23,000 households based on the most recent census from the National Statistics Department (NSD) [22], though the population can increase to 300,000 people during long weekends and high season holidays (June to July and December to January). Between 5 and 12 October 2015, a national beauty pageant in Girardot drew tourists from all regions in Colombia. Girardot is 289 m above sea level. The average temperature is 33.3 °C, and the relative humidity is 66%. The mean annual precipitation is 1,220 mm with a rainy season extending from May through October [23]. The most productive breeding sites of *Ae. aegypti* in Girardot are unprotected private water containers, such as water storage tanks used in the households during the dry and rainy seasons, while public spaces provide more breeding sites during the rainy season [24]. Girardot has experienced hyperendemic transmission of dengue since 1990 with simultaneous circulation of all four serotypes; the mean annual incidence was 5.72 per 1,000 inhabitants between 1999 and 2010 [19]. In late 2014, CHIKV started circulating in Girardot and that year it reached an annual incidence of 3.94 per 1,000 inhabitants, while in 2015 the annual incidence was 4.97 per 1,000 inhabitants [21,25].

Case definition and laboratory analysis

We analysed surveillance data from nine local healthcare sites in San Andres and twenty-two local healthcare sites in Girardot, representing 100% of surveillance sites in both locations. Standardised case definitions used in both areas were defined by the Ministry of Health (MoH) and Colombian National Institute of Health (C-NIH) at the beginning of the ZIKV epidemic.

Figure 2

Daily Zika virus disease incidence in San Andres, Colombia, September 2015–January 2016 (n=928 cases)



Cases include all reported cases, which were San Andres residents.

According to these definitions, a suspected ZVD case is a person presenting with body temperature higher than 37.2 °C, maculopapular exanthema, and one or more of the following: arthralgia, headache, malaise, myalgia or non-purulent conjunctivitis and who lived or travelled to an area at risk for ZIKV transmission (usually below 2,000 m above sea level in Colombia) within 15 days of symptom onset. A laboratory-confirmed case is a suspected case with a ZIKV-positive reverse transcription-polymerase chain reaction (RT-PCR) result as determined by the C-NIH virology reference laboratory. ZIKV antibody testing was not done in Colombia due to high cross-reactivity with other endemic arboviruses. A clinically-confirmed case is defined by the Colombian authorities in the same way as a suspected case, except that the area of residence or travel within 15 days of symptom onset is an area with laboratory-confirmed ZIKV circulation [26].

Because the definition of a clinically-confirmed case in Colombia corresponded at the time of the study, to that of a probable case according to the WHO classification, we further refer to clinically-confirmed cases as probable cases in the context of this report [27].

At the start of the outbreaks in Girardot and San Andres, when local circulation of ZIKV had not yet been laboratory confirmed, only suspected cases were reported. Once the C-NIH confirmed the circulation of ZIKV in Girardot (on 27 January 2016, 3 months after the first local case report) and San Andres (on 22 October 2015, 45 days after the first local case report), the samples from suspected ZIKV cases were sent for laboratory confirmation if the respective cases fell into the risk groups defined by the C-NIH, including newborns and infants (age < 1 year), persons aged > 65 years, pregnant women, and individuals with comorbidities (e.g. diabetics, persons who were immunocompromised and/or with cardiovascular diseases) [23].

After ZIKV circulation was confirmed in the two areas, suspected cases whose acute samples tested positive were reclassified as laboratory-confirmed cases, while those with samples negative for ZIKV were reclassified as non-cases [26]. All reported suspected cases, who had not undergone laboratory testing were reclassified as probable cases [27].

Data collection

The data in San Andres were collected initially using the C-NIH standard report form for dengue surveillance because from September up to October 2015 the outbreak in San Andres had an unknown aetiology. Once the C-NIH declared an alert on 14 October 2015 because ZIKV circulation had been observed in other areas of Colombia, reporting of ZVD became mandatory in the country, after which cases were reported by physicians at the healthcare sites using the standard report form for ZVD surveillance. The completeness of reporting is not known. We analysed a de-identified dataset based on place of residence with the following variables: age, sex, pregnancy status, date of symptom onset, date the case visited the healthcare facility, date the case was reported to the national surveillance system, and case type (suspected, laboratory confirmed, probable). Non-residents were excluded from the data [28].

Statistical analysis

We calculated overall and age/sex-specific attack rates using population census data from NSD [22].

Figure 3

Age- and sex-specific Zika virus disease attack rates for San Andres, Colombia, September 2015–January 2016 (n=928 cases)

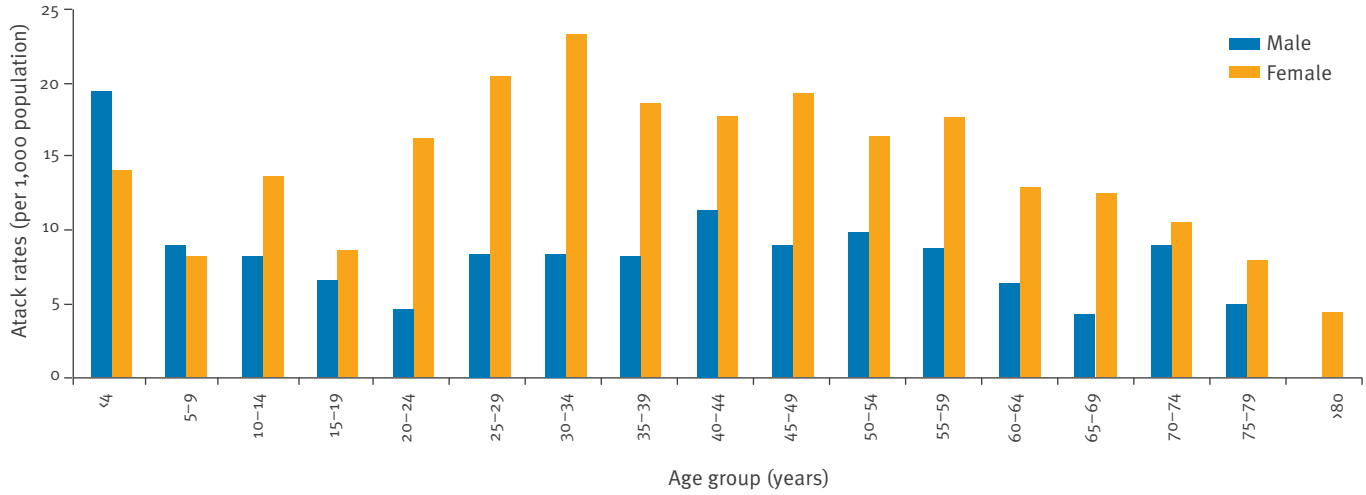
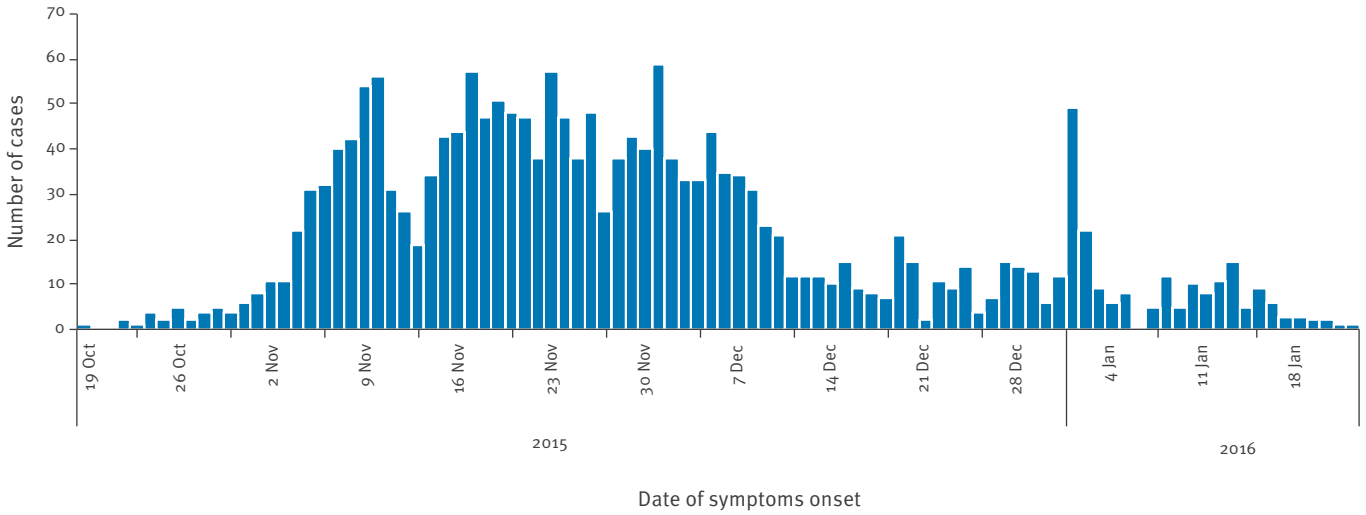


Figure 4

Daily ZVD incidence for Girardot, Colombia, October 2015–January 2016 (n=1,936 cases)

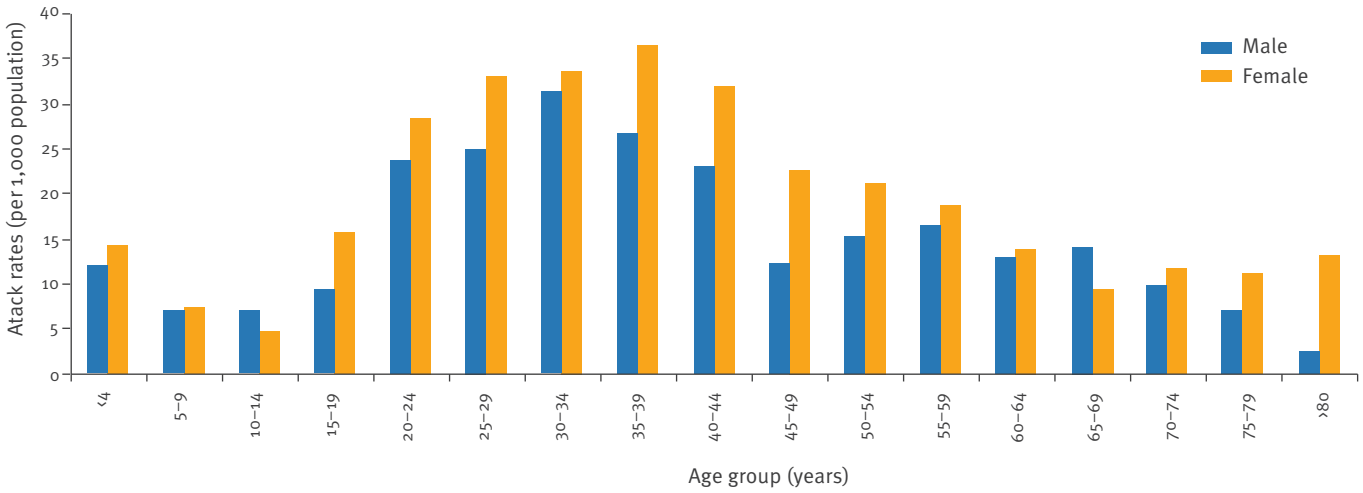


Surveillance data were analysed using R version 3.2.0 [29]. For descriptive results, categorical variables are presented as proportions and continuous variables by the median and interquartile range (IQR) or range. The relationship between attack rates and the variables age and sex was tested using log-linear models for case counts with age category (0–19 years-old, 20–49 years-old and >50 years-old), sex, and an interaction between age category and sex as independent variables, with population size as an offset.

To estimate the basic reproductive number Ro in each population, we used maximum likelihood methods to fit a chain-binomial model to daily incidence data [30]. The model assumes a mean serial interval of 22 days (time between successive cases in a chain of transmission); the serial interval takes into account the infectious period in humans, the extrinsic latent period in mosquitoes, the mean infectious period in the mosquito, and the mean incubation period in humans [4,9,31,32]. Underreporting is assumed to be high (only 10% of cases reported) at the start of the outbreak and full reporting is assumed to be achieved in four weeks after the outbreak begins to grow. With this assumption, we aimed to take into account the respective delays in the two sites, between the ZVD outbreak start and the confirmation by the C-NIH of circulation of ZIKV. Ro is the median effective reproductive number during the growth phase of the epidemic, after accounting for early underreporting (see supplementary materials online for additional details on the model: https://github.com/dprojas/Zika).

Figure 5

Age- and sex-specific Zika virus disease attack rates for Girardot, Colombia October 2015–January 2016 (n=1,936 cases)



Results

San Andres

In San Andres, we identified 928 reported ZVD cases (Table 1). Of these cases, 52 (5.6%) were laboratory confirmed by RT-PCR on acute phase samples collected within five days of symptom onset, and 876 (94.4%) cases were probable.

The dates of symptom onset among cases in San Andres ranged from 6 September 2015, to 30 January 2016 (Figure 2). Though the earliest case reported symptom onset on 6 September 2015, the local healthcare authorities did not receive laboratory confirmation of ZIKV until 22 October 2015. The distribution of this outbreak was bimodal. The first wave of the outbreak was before the C-NIH made an alert on 14 October 2015, about circulation of ZIKV in the country. The second wave started after the alert and the number of cases peaked in epidemiological week 45 (8 to 14 November), before the high tourist season started, and subsided in the last week of December. The second wave could be due to a reporting phenomenon.

The median time between symptom onset and visiting a healthcare facility was 4 days (IQR: 1–16).

Around 79% (733/928) of cases were reported to the national surveillance system on the same day that they visited the healthcare facility. The median age of reported ZVD cases in San Andres was 31 years-old (IQR: 15–47 years; range: 12 days–82 years). A total of 589 (63.5%) of the reported cases occurred in females. During the study period 238 dengue cases (incidence rate: 4.36 per 1,000 habitants) and 10 CHIKV cases (0.18 per 1,000 habitants) were reported in San Andres as expected in accordance with the trends and the historical data (data not shown).

The overall attack rate for ZVD reported by local surveillance was 12.13 per 1,000 San Andres residents. The sex-specific attack rates were 15.34 per 1,000 females and 8.91 per 1,000 males; the difference was significant adjusting for age ($p<0.001$). Cases occurred among all age groups, but the incidence of ZVD detected by local surveillance was highest among persons 20 to 49 years-old (Figure 3); there was significant heterogeneity across the age groups ($p<0.001$). There was a significant interaction between age and sex ($p<0.001$), consistent with the observation that attack rates were higher in females across all age groups 10 years-old and above, but lower for the younger age groups (Table 2).

Thirty-three pregnant women with ZVD were reported in San Andres and are being followed according to national guidelines [33,34]. By June 2016, twenty-eight of them had given birth with two probable cases of congenital ZIKV syndrome reported. There were eight neurological syndromes reported in San Andres, including GBS and meningoencephalitis attributed to ZIKV and among them one death was reported. The incidence rate of neurological syndromes among ZVD cases in San Andres is 8.6 per 1,000 cases.

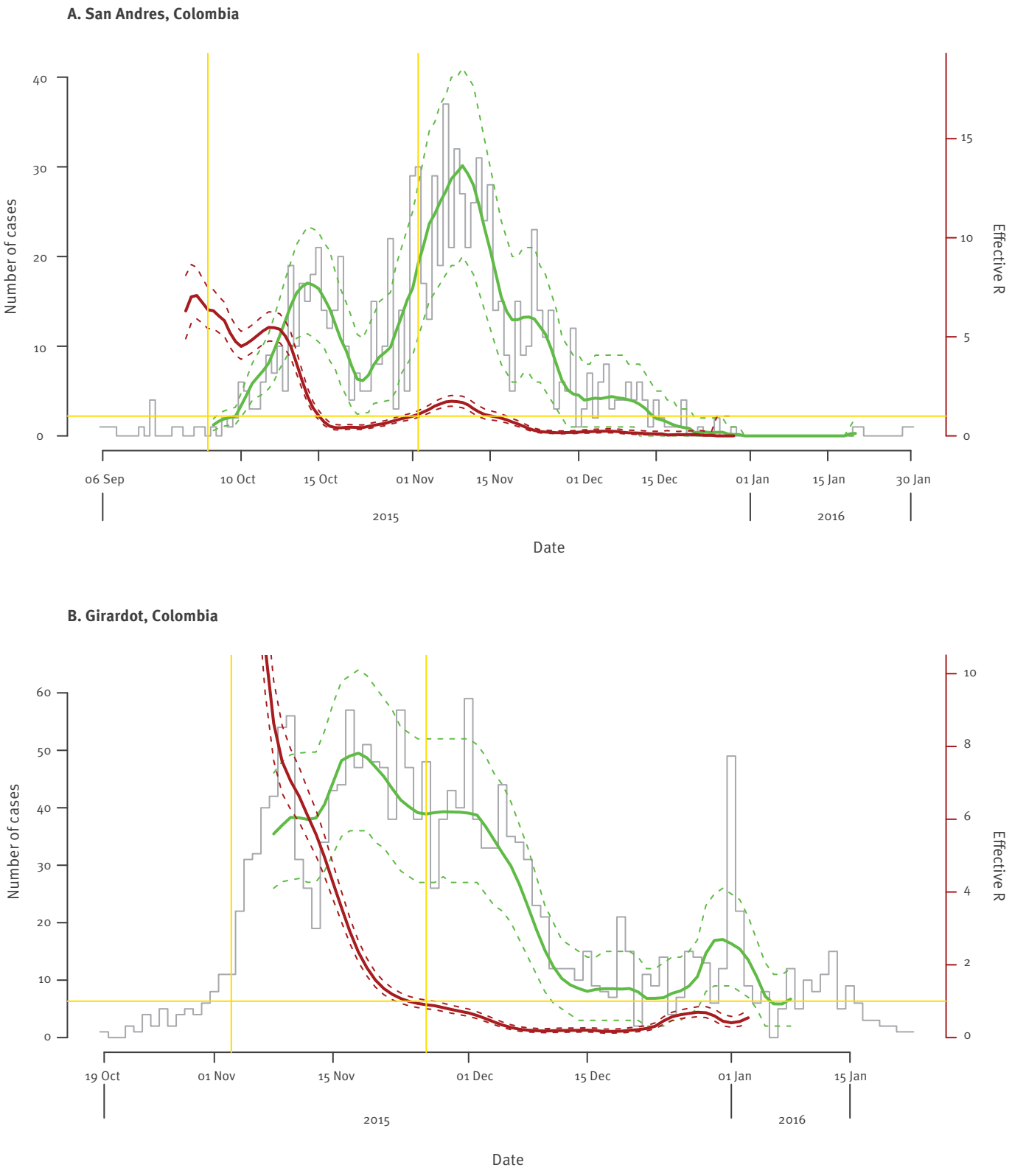
Girardot

In Girardot, we identified 1,936 reported ZVD cases (Table 1). Of these cases, 32 (1.7%) were laboratory confirmed by RT-PCR on acute phase samples collected within five days of symptom onset and 1,904 (98.3%) were probable.

The date of symptom onset among cases in Girardot ranged from 19 October 2015 to 22 January 2016 (Figure 4). The first suspected case was reported on 23 October 2015, 19 days after the beauty pageant event started, with laboratory confirmation obtained on 27 January 2016. The number of cases peaked in epidemiological week 48 (29 November to 5 December) before

Figure 6

Estimates of effective R (red) and model-fitted daily case numbers (green) for outbreaks of Zika virus disease in Colombia, September 2015–January 2016 (n=2,864 cases



CI: confidence interval; Ro: basic reproductive number.

(A) Estimates of effective R (red) and model-fitted daily case numbers (green) for the outbreak of ZVD in San Andres, Colombia. The proportion of cases reported is assumed to increase linearly from 10% on and before 30 September 2015, to 100% in 4 weeks. Dashed curves (both red and green) are conservative 95% CIs. Histogram in grey shows the epidemic curve. The horizontal yellow line indicates the reference value of 1. The two vertical yellow lines indicate the time interval used for the estimation of Ro.

(B) As (A) for Girardot, Colombia. The proportion of cases reported increases on 19 October 2015.

Table 1

Characteristics of reported cases of Zika virus disease in two areas of Colombia, September 2015–January 2016

Areas	San Andres	Girardot
Total number of cases	928	1,936
Laboratory confirmed cases n (%)	52 (5.6%)	32 (1.7%)
Probable cases n (%)	876 (94.4%)	1,904 (98.3%)
Female n (%)	589 (63.5%)	1,138 (58.8%)
Median age in years (IQR)	31 (15–47)	34 (24–46)
Median time in days to visit healthcare facility from symptom onset (IQR)	4 (1–16)	1 (1–2)

IQR: interquartile range.

the end-of-the-year tourist season, and subsided in early January.

The median time between symptom onset and visiting a healthcare facility was 1 day (IQR: 1–2 days). Around 89% (755/1,936) of cases were reported to the national surveillance system on the same day they visited the healthcare facility. The median age of confirmed ZVD cases was 34 years-old (IQR: 24–46 years; range: 15 days–92 years). A total of 1,138 (58.8%) cases were female. During the study period 75 dengue cases (incidence rate: 0.73 per 1,000 habitants) and 200 CHIKV cases (1.95 per 1,000 habitants) were reported in Girardot as expected in accordance with the trends and the historical data (data not shown).

The overall attack rate for confirmed ZVD detected by local surveillance was 18.43 per 1,000 Girardot residents. The sex-specific attack rates were 20.53 per 1,000 females and 16.07 per 1,000 males; the difference was significant adjusting for age ($p < 0.001$). Cases occurred among all age groups, but the incidence of ZVD detected by local surveillance was highest among persons 20 to 49 years-old (Figure 5); there was significant heterogeneity across the age groups ($p < 0.001$). Attack rates were higher in females in all age groups except in those 10 to 14 and 65 to 69 years-old; there was no significant interaction between age and sex ($p = 0.20$) (Table 2).

Sixteen pregnant women with ZVD were reported in Girardot and are being followed according to national guidelines [33,34]. By June 2016, twelve of them had given birth with no complications or microcephaly reported. Nine cases with GBS have been reported after an initial suspected ZIKV infection; laboratory-confirmation of ZIKV is pending. There were no deaths attributed to ZIKV. The incidence rate of neurological syndromes among ZVD cases in Girardot is 4.6 per 1,000 cases.

Basic reproductive number calculations

Daily incidence data were used to estimate Ro. The estimated Ro for the Zika outbreak in San Andres was 1.41 (95% confidence interval (CI): 1.15–1.74), and the Ro in Girardot was 4.61 (95% CI: 4.11–5.16) (Table 2 and Figure 6). Odds ratios for sex and age effects were obtained from the likelihood model, indicating increased odds of transmission among females and adults aged 20 to 49 years-old in both San Andres and Girardot (Table 2).

The estimation procedure was also applied to daily incidence data from a published outbreak in Salvador, Brazil, that occurred between 15 February 2015, and 25 June 2015; 14,835 cases were reported with an overall attack rate of 5.5 cases per 1,000 Salvador residents [7]. The estimated Ro of the Zika outbreak in Salvador, Brazil was 1.42 (95% CI: 1.35–1.49).

Sensitivity analyses are reported in the supplementary online materials (https://github.com/dprojas/Zika), including varying the incubation period in humans, the infectious period in humans, the infectious period in mosquitoes, the duration of underreporting, and the level of underreporting at the start of the outbreak.

Discussion

We report surveillance data on ZIKV outbreaks in two areas in Colombia between September 2015 and January 2016. The first area, San Andres, is a small, densely populated island that is relatively isolated from continental Colombia. The second area, Girardot, is a typical moderately sized Colombian municipality. Both regions have endemic transmission of dengue and experienced recent outbreaks of CHIKV. We describe key epidemiological features of the ZVD outbreaks and estimate Ro from daily incidence data.

The overall attack rates for ZVD as detected by local surveillance were 12.13 cases per 1,000 residents of San Andres and 18.43 cases per 1,000 residents of Girardot. These attack rates are similar to those reported from Yap Island (14.3 per 1,000) [3] but higher than those reported in Salvador, Brazil (5.5 per 1,000) [7]. In both areas, significantly higher attack rates are observed among women, especially those of child-bearing age. The Colombian government issued an epidemiological alert in December 2015 to actively search for pregnant women with ZVD-like symptoms in areas with active transmission [33,34]. This effort may partially explain the findings, though differences in sex-specific

Table 2

Estimates of basic reproductive number (R_0), sex-specific odds ratios (OR) and age-specific OR for transmission of Zika virus disease in San Andres and Girardot, Colombia, September 2015–January 2016

Parameter Estimate (95%CI)		San Andres	Girardot
		Estimate (95%CI)	
R_0		1.41 (1.15–1.74)	4.61 (4.11–5.16)
OR sex	Male	Reference	Reference
	Female	1.71 (1.50–1.95)	1.28 (1.17–1.40)
OR age in years	20–49	Reference	Reference
	0–19	0.86 (0.74–0.99)	0.37 (0.33–0.42)
	>50	0.74 (0.63–0.88)	0.46 (0.41–0.52)

CI: confidence interval.

attack rates persist when only cases occurring before December are considered. These results could be explained by male-to-female sexual transmission of ZVD, which is consistent with higher attack rates in females beyond child-bearing age. Given recent evidence from Brazil, in areas with ZIKV transmission, interventions aimed at preventing sexual-transmission of ZIKV to women are necessary because this mode of transmission could have a substantial influence on the overall dynamics of ZIKV epidemics [35-37]. Cases occurred in all age groups, but the most affected age group was 20 to 49 year of age, similar to previously published outbreaks in Yap Island, Micronesia, and in Salvador, Brazil [3,7]. As the population was fully susceptible to ZIKV transmission before the outbreaks, it is expected that all age groups would be affected.

Forty-nine pregnant women with ZVD were reported from San Andres and Girardot. These women are being followed according to national guidelines [33,34] with two probable cases of congenital ZIKV syndrome reported from San Andres to the national authorities for analysis. Seventeen cases of neurological syndrome, including GBS and ZIKV-associated meningoencephalitis, were identified, similar to reports from French Polynesia and Brazil [12,38]. Laboratory-confirmation of these cases is challenging because neurological symptoms generally appear two weeks after acute symptoms [39] at which time ZIKV diagnosis by RT-PCR is not possible and serological tests are unreliable because of cross-reactivity with dengue [40,41]. As ZIKV can be detected in urine longer than in serum [42], using urine samples to confirm ZIKV in GBS cases may be an alternative [43]. These challenges underscore the need for reliable diagnostic tests that can detect ZIKV after the viraemic period.

In each area of this study, daily incidence data were used to estimate Ro. Our estimated Ro for the ZVD outbreak in San Andres was 1.41 (95% CI: 1.15–1.74), and the Ro for Girardot was 4.61 (95% CI: 4.11–5.16). Applying the same methods with previously published data, we estimated that the Ro for ZIKV in Salvador, Brazil, was 1.42 (95% CI: 1.35–1.49) [7]. We consider the estimate from San Andres to be the most reliable because it is a small, densely populated island and the outbreak occurred before the national epidemiological alert, while Girardot has a higher risk of importation because the population fluctuates during weekends and holidays. The relative magnitudes of Ro are consistent with the higher dengue transmission historically observed in Girardot vs San Andres [19].

Estimates of Ro in ZIKV are not widely available, though reports suggest an Ro of 4.3 to 5.8 in Yap Island and Ro of 1.8 to 2.0 in French Polynesia [44]. A recent manuscript considering the French Polynesian outbreak reported a range from 1.9 to 3.1 [45].

Relatively few cases were laboratory confirmed. One limitation of this study is that the majority of cases were probable, and the symptoms could be caused by other aetiologies such as dengue or CHIKV. Nonetheless, in the field we have observed that the diseases have different clinical manifestations. Dengue appears to coincide with high fever (>38.5 °C), headaches, myalgia, and generalised pain. CHIKV is associated with joint pain and arthritis, and ZVD is associated with a very mild, low-grade fever (38 °C) or no fever, rash, and no generalised pain. This report only includes symptomatic cases who attended a healthcare facility and were captured by the surveillance systems. ZIKV usually causes a relatively mild illness lasting several days, and around 80% of infections are currently believed to be asymptomatic, so we are likely missing many mild or asymptomatic cases [10]. We also do not have a reliable estimate of underreporting at the study sites. Early underreporting seemed to be especially apparent in the Girardot outbreak compared with San Andres given that the circulation of ZIKV was not confirmed until January, 2016, and the sharp increase in cases in Girardot observed may be due to increased public awareness of the disease. This phenomenon can result in an overestimate of Ro.

Well-designed studies can provide valuable insight. Phylogenetic analyses of circulating ZIKV strains will be critical for understanding whether mutations in the viral genome are associated with an increased severity of disease, as manifested by microcephaly and GBS in this outbreak. Household studies can allow for more accurate estimation of transmission dynamics and enhance understanding of asymptomatic infection. Studies are required to understand the interactions between ZIKV, dengue, CHIKV, and other co-circulating arboviruses and their impact on disease. It is also necessary to increase surveillance of neurological syndromes associated with ZVD, such as GBS and encephalitis.

The evidence for a causal relationship between ZIKV and microcephaly is strengthening [46-48]. Recent evidence from the French Polynesia outbreak suggests

an estimated number of microcephaly cases possibly associated with ZIKV infection is around one per 100 women infected in the first trimester [49]. Currently the Colombian Government is following a cohort of pregnant women that reported ZVD-like symptoms anytime during their pregnancy. Those who are detected during the acute phase are being diagnosed with ZIKV RT-PCR. All women will be followed until the end of pregnancy, and the fetus will be evaluated during pregnancy, with a subsequent post-natal follow-up of twelve months [17]. The prospective collection of data through this and other similar national cohorts will be essential for assessing causality, determining risk factors, and estimating rates of birth defects.

The results of this and other reports conclude that transmission of ZIKV may be widespread. Vector control has had limited success in controlling other arboviruses, such as dengue. A safe and efficacious vaccine, especially for women of child-bearing age, may be needed to reduce the disease burden.

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Conflict of interest

None declared.

Authors' contributions

DPR, NED, YY: Study design, data analysis, data interpretation, figures, writing and approval of this manuscript. EK: Study design, data analysis, data interpretation, approval of the manuscript. JQ, ST, ELR, YK, CC, GC: Data collection, data analysis, data interpretation, approval of this manuscript. MEH and IML: Study design, data analysis, data interpretation, writing and approving this manuscript.

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