EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

MISSION REPORT

CHIKUNGUNYA IN ITALY

Joint ECDC / WHO visit for a European risk assessment
17 – 21 September 2007

ecdc.europa.eu

ACKNOWLEDGEMENTS

This visit was carried out by a group of European experts with extensive experience in the epidemiology and diagnosis of chikungunya infection, as well as in the surveillance and control of the vector. ECDC sincerely thanks these experts for their availability and for their active contribution during the visit, which ensured the high quality of this risk assessment.

We would also like to thank the Italian health authorities for their constructive and transparent collaboration over the course of this visit, as well as before and after in the development of the European risk assessment following the chikungunya outbreak in Italy. In particular, we want to thank the regional and local health authorities of the Emilia-Romagna region and of the province of Ravenna, for their availability and openness during our visit, and for their remarkable commitment in the response to the outbreak. We thank the experts on national level, both from the Istituto Superiore di Sanità and the National Institute for Infectious Diseases 'Spallanzani', for their availability and expert input in the European risk assessment. We also want to thank the national Ministry of Health for their warm welcome and willingness to share the experience of this first outbreak on the European continent.

Most of the epidemiological data represented in this report were kindly provided by the local, regional and national Italian health authorities, for which ECDC is extremely grateful; these data were essential for ensuring a successful risk assessment on European level.

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1. BACKGROUND

On 30 August 2007, the italian Ministry of Health, through the Early Warning and Response System (EWRS) and under the revised International Health Regulations (IHR) (2005), notified the EU Member States, the European Centre of Disease Prevention and Control (ECDC) and the IHR contact point of the World Health Organization (WHO) regional office for Europe, of a laboratory-confirmed outbreak of chikungunya fever in the region of Emilia-Romagna in north-eastern Italy. At the time of notification, 131 suspected cases had occurred since the first (then known) case with onset of symptoms on 4 July. The majority of cases were reported from two neighbouring small villages (Castiglione di Ravenna and Castiglione di Cervia) in the province of Ravenna.

Upon recognition of a cluster of 47 cases on 16 August, the initial hypothesis had indicated an arboviral fever as the cause of the outbreak, possibly sandfly fever. Considering the suspicion of vector-borne origin of the outbreak, vector control measures (adulticides) were implemented on 18 August in the affected area. The absence of sandflies in the traps ruled out sandfly fever. Chikungunya fever was suspected based on the symptoms presented by the initial cases and on the presence of large numbers of *Aedes albopictus* mosquitoes in the traps. On 29 August, chikungunya fever was confirmed by laboratory testing.

The outbreak of chikungunya fever in north-eastern Italy is the first documented local vector-borne transmission of Chikungunya virus within the European main land. Considering the presence of the vector *Aedes albopictus* in other EU countries, and therefore the risk of spread to these areas, the italian health authorities agreed on a joint ECDC/WHO visit, to assess the risk of establishment of local transmission and spread to other EU regions. In order to ensure an optimal outcome of the visit, ECDC invited international experts in epidemiology, virology and entomology, with specific experience in investigating and controlling chikungunya fever outbreaks.

2. OBJECTIVES OF VISIT

The objectives of the visit were:

- to assess the risk of establishment and spread of Chikungunya virus transmission in the EU following the establishment of local transmission in the provinces of Ravenna and Forlì-Cesena in north-eastern Italy;
- to explore its potential implications for the EU and other European countries;
- to advise italian health authorities on investigation and control issues.

The team spent two days in the Emilia-Romagna region where it met with the local and regional health authority and visited the affected areas (Ravenna and Forlì-Cesena provinces) in order to gather relevant information at the local and regional level. It then spent three days in Rome meeting with the Ministry of Health and experts involved in surveillance and control activities at the Istituto Superiore di Sanità (ISS) and Istituto Nazionale Malattie Infettive Lazzaro Spallanzani (INMI) (see Annexes 1 and 2).

3. MAIN FINDINGS

3.1. Epidemiological situation

Time line: epidemic curve

Between 15 June and 21 September, a total of 292 suspected cases were reported, 125 of whom had been confirmed at the time of the visit. The chikungunya outbreak started in Castiglione di Cervia and Castiglione di Ravenna, two small neighbouring villages in the province of Ravenna, separated by a small river. These villages are situated 6 km from the Adriatic coast, and together have a population of 3 767. The index case of the epidemic is presumed to be a resident of the region, who travelled to the state of Kerala, India, in June, and presented with two episodes of fever on 15 June and 23 June. During the second fever episode, he visited his cousin in Castiglione di Cervia for several hours. The cousin, the second reported case, had an onset of symptoms on 4 July.

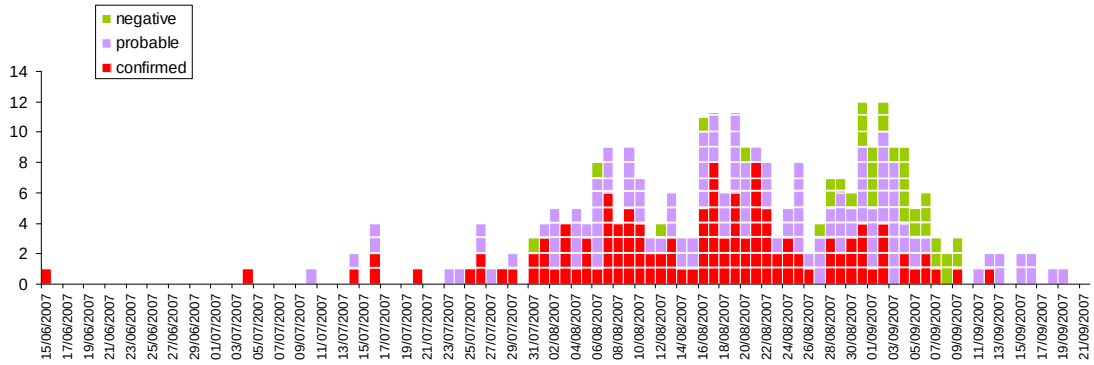

Figure 1. Distribution of suspected chikungunya fever cases by date of onset of symptoms, region of Emilia-Romagna, 15 June - 21 September 2007 (n = 292)

The epidemic curve (figure 1) shows the presumed index case with onset of symptoms on 15 June, followed by waves of subsequent cases, compatible with a secondary vector-borne transmission. As the epidemic curve is presented by onset of symptoms, the decreasing number of reported cases in the most recent two weeks may be partly due to delays in cases seeking medical attention and being reported.

Retrospective testing of cases was initiated recently, explaining the significant proportion of early cases still awaiting results (depicted as probable cases).

Geographical extent

The outbreak spread throughout the two villages of Castiglione di Cervia and Castiglione di Ravenna, affecting residents and a small number of persons who came to visit family or friends. However, since the end of August, cases with no known potential exposure in the two Castiglione villages have been reported, providing evidence of local transmission in adjacent areas. These include, based on the currently available information, Cervia, Cesena, Ravenna and Rimini where one confirmed case was reported with onset of symptoms on 12 September (figure 2). In addition, in spite of strong vector control activities, transmission of Chikungunya

virus was still ongoing during the third week of September in the original two affected villages of Castiglione di Cervia and Castiglione di Ravenna, where a few recent, confirmed cases had been reported (date of onset 6 September).

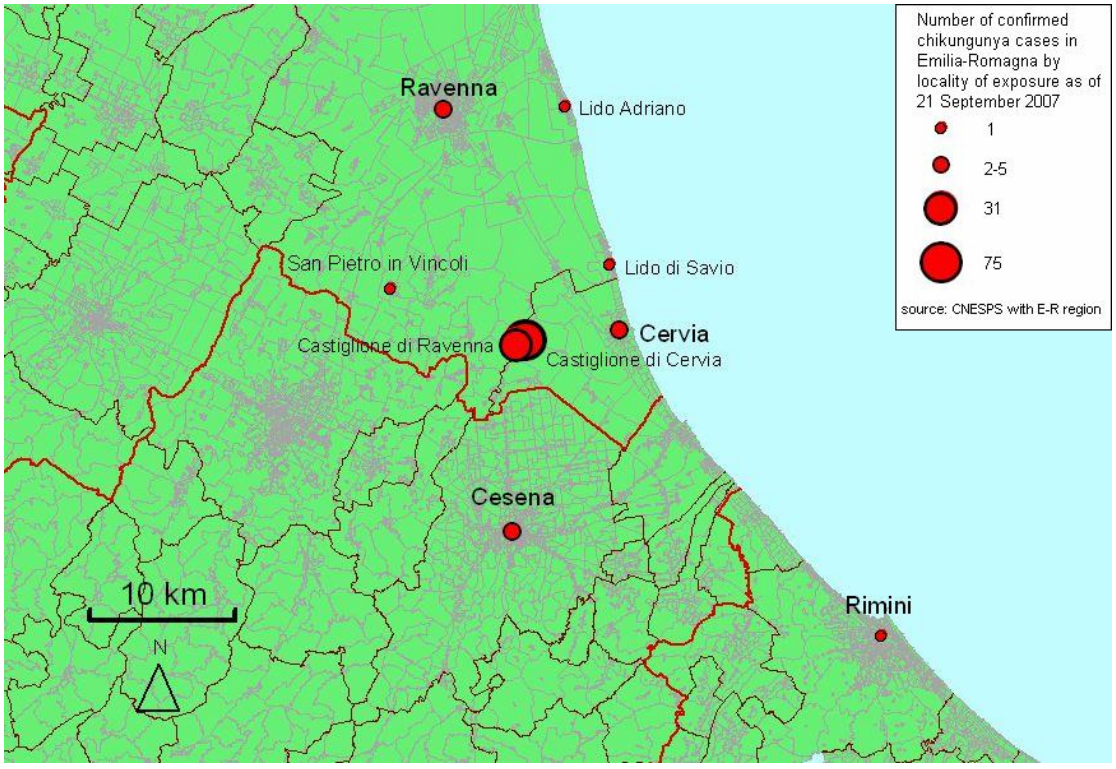

Figure 2. Distribution of confirmed cases of chikungunya fever by locality of exposure, region of Emilia-Romagna, as of 21 September 2007 (n = 125)

A total of 10 additional suspected cases have been reported from three other regions, but all travelled to Emilia-Romagna and were therefore potentially exposed there. These cases, awaiting laboratory confirmation, are not included in the total reported.

Persons affected

The median age of cases is 59 for confirmed cases, ranging from 3 to 95; and 53 for suspected cases, ranging from 1 to 92. This apparent over-representation of older persons is potentially explained by the rural nature of the two initial villages where most cases occurred. However, a reporting bias (older people seeking medical care more often), a severe clinical presentation or a higher exposure to mosquitoes in this age group cannot be excluded. The male to female ratio is 0.83.

The symptoms presented by the confirmed cases are similar to those presented by cases during the outbreak in La Réunion, with 95% of arthralgia.

One 83 year-old patient, presenting with underlying conditions, died. One patient is currently comatose; both PCR tests for viral RNA in the liquor turned out negative.

Surveillance activities

Following the initial warning by a citizen of Castiglione di Cervia on 9 August, the local health authorities contacted the Ravenna hospital as well as general practitioners of Castiglione. On August 14, 47 suspect cases had been identified through this active case search. On August 20, blood samples were collected. On 24 August, epidemiological surveillance was extended to all general practitioners in the province, inviting them to report all suspected cases on the basis of high fever, joint pains, asthenia and/or rash, having stayed in the two affected villages (even if only for a few hours) or with a history of travel abroad in endemic areas.

As from 29 August, in order to closely monitor the epidemiological situation, the health authorities of the Emilia-Romagna region developed the following criteria for active surveillance purposes, based on the general practitioners and hospital emergency units:

- **Clinical criteria**: acute onset of fever (>38.5˚C) and severe arthralgia not explained by other medical conditions.
- **Epidemiological criteria**: residing or having visited epidemic areas, having reported transmission within 15 days prior to the onset of symptoms.
- **Laboratory criteria**: at least one of the following tests on a blood sample in the acute phase:
  - virus isolation;
  - presence of viral RNA by RT-PCR;
  - presence of virus-specific antibodies in single serum sample collected.

On this basis, the following case definitions were used:

- **Possible case**: a patient meeting clinical criteria.
- **Probable case**: a patient meeting both the clinical and epidemiological criteria:
  - **national probable case**: a patient meeting the clinical criteria and exposed in one of the provinces affected by transmission of Chikungunya virus,
  - **local probable case**: a patient meeting the clinical criteria and exposed in one of the municipalities affected by transmission of Chikungunya virus.
- **Confirmed case**: a patient meeting the laboratory criteria, irrespective of the clinical presentation.

The term suspect case has been used for both possible and probable cases awaiting laboratory confirmation. A suspect case is classified **negative** if:

- RT-PCR is negative on samples collected within the first five days following onset of symptoms; or
- Serology test is negative on samples collected 6 days or more after onset of symptoms.

3.2. Entomological situation

Aedes albopictus in Italy

In response to the reported presence of *Aedes albopictus* in Genoa (Liguria region) in 1990, a surveillance and control programme was established by the Ministry of Health, under the coordination of the ISS. In 1992, the establishment of *Aedes albopictus* in the Veneto region

was traced back to the importation of used tyres from Atlanta, Georgia in the USA. The tiger mosquito then reached other italian regions through gradual colonisation of the bordering areas and through short and long distance passive transfer of eggs or different mosquito evolution stages. Guidelines for the control of *Aedes albopictus* were issued by the Ministry of Health in 1994. *Aedes albopictus* was first reported in Rome in 1997. In 1998, it was established in 22 italian provinces in nine different regions.

Aedes albopictus in Castiglione di Cervia and Castiglione di Ravenna

In March 2005, all municipalities of the Emilia-Romagna region received the guidelines for the control of tiger mosquitoes. *Aedes albopictus* is known to be present in the two Castiglione villages since 2006. The two villages are separated by a river with relatively stagnant water resulting from the presence of a lock. Conditions around the houses seem optimal for vector development and expansion. Houses are typically low (two storeys), surrounded by small gardens with many flowers, plants and flower pots (see picture 1, below). In the streets, drainage systems are visible, indicating open stagnant water underground.

Picture 1. Riverbank, Castiglione di Cervia, province of Ravenna, 18 September 2007

Monitoring of vector activity in Emilia-Romagna

The current vector monitoring system comprises 1 800 ovitraps in the region. Up to 2 500 traps are planned to be functional in 2008. Weekly monitoring data are available on a dedicated website (www.zanzaratigreonline.it). Based on current operational evidence, this regional monitoring system is among the most advanced in Italy, and probably in most parts of Europe.

The available data indicated an increase of vector presence in the area over the recent years corresponding to the establishment of the vector in the area, and reached a plateau in 2007. The favourable conditions for local transmission were present in the two Castiglione villages, and it is very likely that such conditions exist in other areas of the Ravenna province and Emilia-Romagna region. The appearance of new cases in Ravenna, Rimini and Cesena, who

had no history of exposure to the initially affected area, suggests that transmission has spread through infected mosquitoes to at least three urbanised areas. This finding needs to be taken into account in the risk assessment, surveillance and response to the outbreak.

Although *Aedes albopictus* activity has been shown all year round (including the winter months) in certain regions of Italy (e.g. Rome), this has not been demonstrated in the Emilia-Romagna region. It was noted that the hatching of mosquito eggs in the region started around 15 April in 2007, earlier than in preceding years following a particularly mild winter season. Mosquito activity is expected to continue until the end of October, but may extend into November according to the weather conditions.

However, even if no adult mosquitoes circulate during winter time, the recent evidence of trans-ovarian (vertical) virus transmission gained from studies done in la Réunion possibly increases the risk for re-appearance of infected mosquitoes in the spring of 2008. Timely detection of this potential re-appearance through surveillance, with rapid implementation of vector control measures in close collaboration with the local population, will be essential to control a potential recurrence of the virus in 2008.

Control measures implemented

Since 18 August, vector control measures have been implemented in the two villages of Castiglione di Cervia and Castiglione di Ravenna, and were gradually extended as the outbreak progressed. Measures include both the control of breeding sites and the use of insecticides. In addition to targeting public areas, door-to-door control activities are implemented within a radius of 100m around each suspected case, or within a radius of 300m around every cluster of cases. Private companies carry out the vector control measures, under the supervision of entomologists from the regional public health service.

3.3. Impact on blood transfusion and transplant activities

Blood donation

On 31 August, blood donation from people living in the municipalities of Ravenna and Cervia was suspended until further notice through a ministerial circular. In addition, people who had stayed in affected areas were suspended from donating blood for 21 days after leaving the area. On 3 September, exclusion measures were extended to Cesena and Cesenatico. It is estimated that these measures are currently preventing 2 100 blood donations per month in suspended areas and 400 per month due to history of travel to areas of potential exposure. Since the region supplies blood to other regions in the country, the impact of these measures is important.

If the outbreak continues or spreads, the blood and plasma self-sufficiency of the region cannot be guaranteed.

Donation and transplantation of organs and tissues

The following measures were implemented on national level:

- **Donation of tissue from cadavers**: donation is not allowed from:

- any people coming from, or having been to (even for a few hours), areas affected by the epidemic, during the four weeks prior to donation;
- any people who acquired chikungunya infection during the six months prior to donation;
- people with present chikungunya infection.

- **Donation of organs from cadavers**: donation is not allowed from:
  - any people coming from, or having been to (even for a few hours), areas affected by the epidemic, during the three weeks prior to donation;
  - any people who acquired chikungunya infection, for the three weeks following fever remission;
  - people with present infections,

  however, for donors without present infection, the donor can be assessed as suitable, provided molecular tests are performed that are able to exclude the infection. In such situations, national expert advice should be sought.
- **Living tissue donors**: for asymptomatic donors coming from, or having been to, epidemic areas, a four-week quarantine period of donated tissue is required as well as clinical observation of the donor. If after this period, no clinical signs are noted, the tissue is allowed to be released.
- **Umbilical cord donation** and cord collection for autologous and allogenic use is not allowed for parturient women living in endemic areas.
- **Umbilical cord donation** as well as collection for allogenic use is not allowed for parturient women who, regardless of the area of residence, have stayed even for a few hours in endemic areas during the three weeks before delivery.

4. RISK ASSESSMENT FOR EUROPE

The current outbreak of chikungunya in Italy is the first documented vector-borne transmission of the virus in continental Europe. The autochthonous transmission has extended beyond the initial two villages, resulting in the establishment of at least three secondary transmission foci by local mosquitoes.[1] In addition, the transmission in the two initial villages had not yet ceased at the time of our visit, more than two months after the initial case occurred.

The importance of this event should not be underestimated and its comprehensive documentation is crucial to ensure a maximal benefit to control its spread and for future preparedness for similar occurrences of mosquito-borne disease transmission, both in Italy and elsewhere.

Risk for sustained virus transmission of Chikungunya virus in Italy

Several factors seem to have contributed to the establishment of local transmission in continental Europe:

[1] Areas of local transmission are defined as the 4th administrative level (considering the country level as the first) in which two or more chikungunya cases were identified with no epidemiological link.

- The high density of *Aedes albopictus* in an area of the Emilia-Romagna region where it had appeared relatively recently and was therefore not yet covered by the vector monitoring system.
- An ecological situation favourable for the development of the vector and for virus transmission, considering the dense local vegetation and domestic backyards with plant pots and potential water containers in the two villages.
- The introduction of the virus by a visitor returning from a chikungunya high endemic area.
- Sufficient (human) population density.

Based on the available data, it is likely that the transmission of Chikungunya virus will persist in the coming weeks, probably until the end of October 2007 when the local vector activity should disappear. This may result in additional chikungunya fever cases occurring and being reported until then.

It cannot be excluded that, in the event of a particularly mild winter, local vector activity may persist during the winter, especially in urban settings, potentially resulting in few sporadic cases which would, however, maintain mosquito-to-human transmission cycles until the spring.

In addition, considering the existence of vertical (trans-ovarian) transmission, reported 'in natura' in a tropical region, mosquitoes infected with Chikungunya virus may re-appear in the spring of 2008, when mosquito eggs hatch and vector activity starts again after the winter.

Finally, the successful establishment of local transmission in continental Europe has shown that the *Aedes albopictus* vector is indeed a competent and capable vector for the transmission of Chikungunya virus in Europe, as was the case on the French island of La Réunion in 2005–06. This confirms the conclusion of the risk assessment for Europe performed by ECDC in March 2006 and stresses the likelihood of further introduction and establishment of local transmission foci in areas where the vector is present.

Risk for further introduction and establishment of Chikungunya virus transmission in the EU

Many visitors have returned from endemic areas and developed chikungunya viraemia in the past. However, such importation of the virus through viraemic patients tended to occur during winter months as most of the affected areas were located in the southern hemisphere. The extension of the epidemic to the Indian sub-continent since late 2006 increases the likelihood that the virus will be re-imported in the future during peaks of the vector activity for Europe.

Aedes albopictus is established in large parts of Europe (see figure 3). The favourable circumstances that allowed the outbreak to occur in Italy after virus introduction may be repeated in other parts of Italy as well as in other Member States where *Aedes albopictus* is already present. Therefore, the current epidemic is a unique opportunity for better understanding of the risk factors and virus and vector dynamics, in order to allow for appropriate preparedness on the European level to prevent or limit future outbreaks.

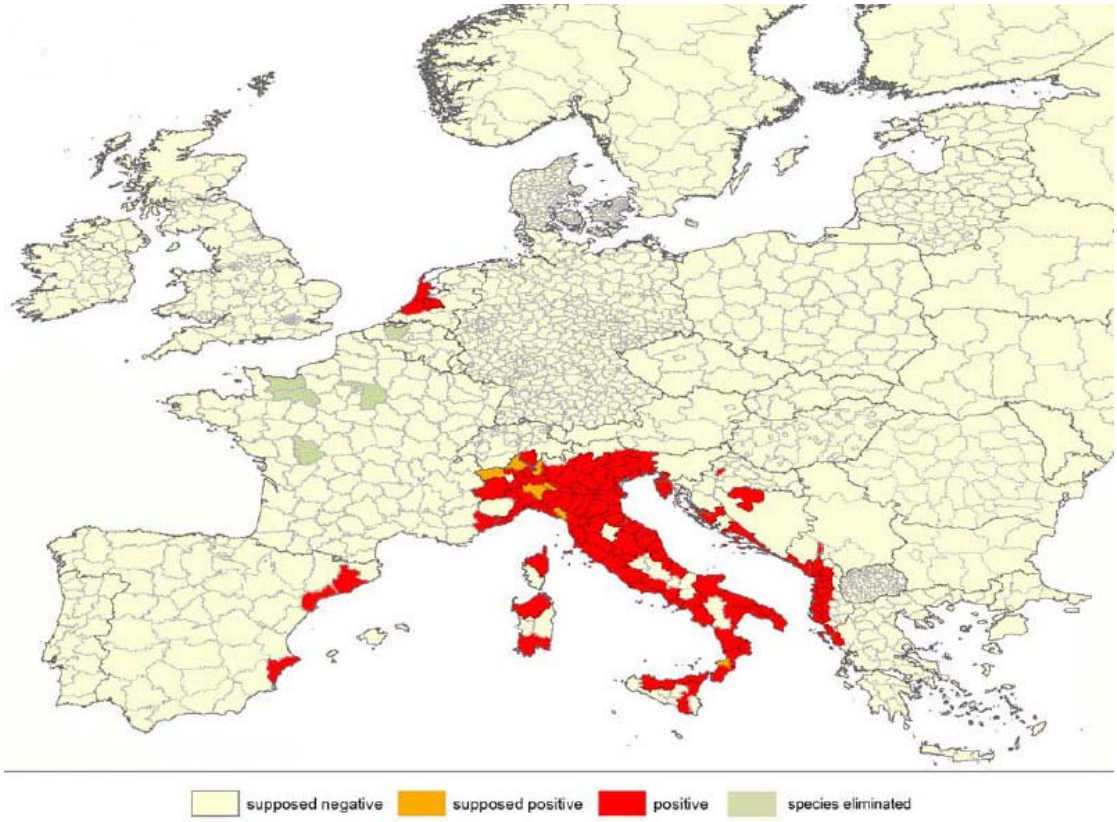

Figure 3: Presence of *Aedes albopictus* in Europe, per province, as of January 2007.[2]

In order to estimate the risk for the establishment of Chikungunya virus transmission in the coming years in the EU, at least two issues need to be addressed.

Firstly, the available data on the presence of *Aedes albopictus* in Europe are incomplete, and the comparability of the data is uncertain. For some areas where the vector could be expected, no data are available. Therefore, the implementation or the strengthening of vector monitoring activities in these areas would be useful to provide updated risk information. In areas where the vector is known *not* to be present, but could possibly be established based on climatic and ecological conditions, the early identification of its introduction will facilitate its control, and possibly even prevent its establishment. Once *Aedes albopictus* is known to be established in an area, it is difficult (not to say impossible) to eradicate the mosquito. Therefore, appropriate measures to limit vector activity need to be implemented.

Secondly, a better understanding of the key determinants for vector establishment will allow the design of more reliable risk maps for the establishment of *Aedes albopictus* in Europe.

[2] Data to complete this figure were kindly made available by Roberto Romi (Italy), Roger Eritja and David Roiz (Spain), Eleonora Flacio (Switzerland), Charles Jeannin (France), Anna Klobučar (Croatia), Zoran Lukac (Bosnia and Herzegovina), Igor Pajovic and Dusan Petrić (Serbia and Montenegro), Bjoern Pluskota (Germany), Anna Samanidou-Voyadjoglou (Greece). Map made by Patrizia Scholte-Scarpulla.
Source: Scholte E-J & Schaffner F, Waiting for the tiger: establishment and spread of the *Aedes albopictus* Mosquito in Europe. In Emerging pests and vector-borne disease in Europe (Takken W. & Knols B.G.J., Eds.), 2007, Wageningen Academic Publishers, Wageningen, The Netherlands, in press.

Climate, humidity and light are some factors influencing the establishment of the mosquito. A more complete understanding of such factors, as well as data collected from areas where it is present, could feed the development of mathematical models predicting the geographical spread of *Aedes albopictus*.

Finally, thorough documentation of the chikungunya outbreak in Italy will improve understanding of the determinants of arbovirus transmission in Europe in general, and help to limit the risk of introduction of other arboviruses transmitted by *Aedes albopictus*, including dengue. Dengue, being distributed worldwide and causing extensive and recurrent outbreaks, is one arboviral disease with an important public health impact.

5. CONCLUSIONS

It is rather fortunate that the chikungunya outbreak in Italy occurred relatively late in the mosquito season; while new cases will continue to be reported, it is likely that the current outbreak will fade out in the coming weeks. At the same time, it is now certain that Chikungunya virus can be transmitted in Europe, and public health authorities need to address this new situation and be prepared for the possibility of reappearance of virus transmission in the spring of next year. This may happen through different scenarios. The persistence of the virus during the winter period, through the survival of infected adult mosquitoes, is a possibility, even though doubtful. Vertical transmission has been shown to occur 'in natura' in a tropical climate. It could possibly cause the re-emergence of Chikungunya virus in the spring of 2008, when vector activity starts again. Finally, the virus could also be reintroduced through international travel, a possibility that applies to all EU countries where *Aedes albopictus* is present.

Virus transmission in Europe is possible, not only in rural villages, but also in urban settings. Therefore, it is important that the winter period is used to prepare as much as possible for the re-emergence of the virus, in all areas in Europe where the vector is present. Early detection of the first cases is crucial to limit the expansion of new transmission cycles. Key factors in preventing large outbreaks are:

- awareness of clinicians about the disease and its risk factors;
- strengthened surveillance systems and rapid notification;
- education and collaboration of the general public in the control of mosquito breeding sites;
- rapid implementation of vector control measures around each case; and
- strengthened vector monitoring systems.

Apart from chikungunya, it needs to be reminded that *Aedes albopictus* is also a vector for other viruses, including dengue virus. Its competence and capacity for transmitting dengue virus is assumed to be less obvious, although renewed research in this area would be useful. Continued awareness for similar re-emerging diseases is needed to ensure rapid detection and control. Additional risk assessments and studies are needed to further characterise the risk for chikungunya and other diseases transmitted by *Aedes albopictus* in Europe. They should be planned and facilitated through active exchange of experience between Member

States, and fostered by addressing related questions in future operational and research projects.

6. NEXT STEPS

The next steps for action include different areas of work. With regards to the epidemiological situation in Europe, the outbreak in Italy as well as the international spread of chikungunya will continue to be monitored closely. Based on all currently available knowledge on the clinical characteristics and the epidemiology of the disease, the virus and the vector, the European risk assessment needs to be updated. The forms for reporting on European level are suggested in Annex 6; these are to be completed with a short protocol on the monitoring of confirmed cases.

The coming winter months should be used in an optimal way to strengthen preparedness of European countries for the re-emergence and/or re-introduction of Chikungunya virus, in particular those countries where *Aedes albopictus* is present or could become established. For this reason, ECDC will organise an expert meeting with European entomologists, in order to define the vector-related determinants for transmission of Chikungunya virus, and make recommendations for refining the risk-mapping for the vector. Preparedness for regions where the vector is present will include strengthening vector monitoring and raising awareness of both health professionals and the public once the vector activity re-starts in the spring of 2008. In areas where the conditions for vector establishment exist, the emphasis will need to be put on early detection of vector introduction, in order to avoid or limit its establishment.

Finally, this visit report will be shared with all stakeholders who may play a role in the further strengthening of the response to Chikungunya virus introduction in Europe. These include the European Commission in encouraging the preparedness of the Member States and funding relevant research projects, including the follow-up of policy implications related to blood donation and organ transplantation, the European Medicines Agency (EMEA) with regards to the development of a vaccine for chikungunya fever, and the European Environment Agency (EEA) regarding the impact of short- and long-term insecticide use on the population and the environment.

ANNEX 1. PARTICIPANTS TO THE MISSION

Jean-Claude Desenclos	Institut de Veille Sanitaire, France
Hervé Zeller	Institut Pasteur, France
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Thomas Seyler	EPIET fellow, Italy
Denis Coulombier	European Centre for Disease Prevention and Control
Evelyn Depoortere	European Centre for Disease Prevention and Control

ANNEX 2. MISSION PROGRAMME

Monday, 17 September	Emilia-Romagna regional and Ravenna local health authorities
	Field visit Castiglione di Cervia and Ravenna
Tuesday, 18 September	Emilia-Romagna regional health authorities
	Press conference
	Final debriefing and conclusions
	Travel to Rome
Wednesday, 19 September	Ministry of Health, Rome
	National Institute for Infectious Diseases 'Spallanzani'
Thursday, 20 September	Department of infectious, parasitic and immuno-mediated diseases, Istituto Superiore di Sanità
	National blood centre and national transplant centre, Istituto Superiore di Sanità
Friday, 21 September	National centre for epidemiology, surveillance and health promotion, Instituto Superiore di Sanità,
	Including final debriefing with the Ministry of Health

ANNEX 3. ECDC GENERAL GUIDANCE ON THE RESPONSE TO CHIKUNGUNYA VIRUS INTRODUCTION IN EUROPE

1. Case detection

Early detection of cases is an essential factor to limit the spread of virus transmission in an area where the vector is present. Therefore, the implementation of a reliable and active surveillance system is important in areas where local transmission is known to be present, or suspected to be possible. In the Emilia-Romagna region, the daily/weekly contacting of primary health care practitioners (including hospital emergency rooms), in combination with immediate notification of suspected cases, has proved to be an efficient way to ensure rapid identification of new cases.

Locally adapted surveillance system

The surveillance system to be put in place should be adapted to the local situation.

In areas where there is virus transmission and chikungunya cases are occurring, early detection through active case finding is essential to rapidly implement vector control measures, limiting the spread of the outbreak. The difference between imported and local cases needs to be made.

In areas where transmission has occurred before but where no cases are currently reported, awareness among clinicians is needed for them to consider chikungunya fever in the differential diagnosis.

In areas where the vector is present, and where virus transmission could become established (but has not yet), case reporting by clinicians should be sufficient, though awareness of the clinicians needs to be strengthened so that they consider chikungunya fever in the differential diagnosis of fever with incapacitating arthralgia.

Finally, in areas where the vector is not present, routine notification of imported cases can be done. The epidemiological link needs to be ascertained systematically.

Once there is a clinical suspicion of chikungunya cases, the diagnosis needs to be confirmed through laboratory testing, which is addressed below (Annex 3.2). The implications of the diagnosis for the vector control measures are discussed in Annex 3.4.

Case definition

It was agreed that the case definition for surveillance should be sufficiently specific, through the inclusion of *incapacitating* arthralgia (see Annex 4). The experience from France in the Indian Ocean outbreak, as well as currently available data on the clinical presentation of cases, suggest that this will make the case definition specific enough while avoiding overburdening laboratory capacity. If deemed necessary, in-depth interviews of all reported suspected cases by the local health unit could be added to ensure correct application of the case definition.

While the case definition presented in Annex 4 may lack the sensitivity to identify all cases in an area where virus transmission is already established, it is expected to be sufficiently sensitive to detect a new cluster of cases in areas where a new transmission cycle has started.

To assist clinicians, it is useful to complement the case definition with a practical algorithm, including a number of guiding questions for the determination of the 'incapacitating' aspect of arthralgia and the existence of an epidemiological link (see Annex 5). Such an algorithm would provide the rationale for requesting laboratory testing and for immediate reporting of probable cases to local health authorities, in order to link with vector control activities.

Case reporting on national level

The case reporting system in place needs to be simple and straightforward in order to avoid confusion on the number of cases at any given time. A single centralised database (at national level) is probably the best option as soon as cases are occurring in more than one administrative unit. Both confirmed and suspected (i.e. waiting for final classification) cases should be reported to this central database. The confirmed cases provide an indication of the areas of virus transmission, while the suspected cases provide information on the possible magnitude of the outbreak in these areas. Both imported (either through national or international travel) and local cases need to be documented.

Rapid communication on the number of cases, the suspected areas of transmission, as well as on the residence of cases is important to avoid, as far as possible, the circulation of false rumours. When communicating case numbers, it should be taken into account that the number of probable and possible cases will vary and can even decrease as the laboratory test results become available. A common web-based database providing access to the different partners could be considered.

Case reporting on the European level

On the European level, only confirmed cases are useful to be reported to ensure permanently updated information on areas where virus transmission occurs and therefore ensuring timely information to European travellers. Depending on the magnitude of the outbreak(s), affected Member States could report individual cases through a simplified line listing reporting form, or – if the outbreak is too large – aggregated data reporting would suffice. Examples of both reporting forms are in Annex 6.

Timely reporting of newly confirmed cases that have no epidemiological links to a known area of transmission is important as it may indicate the establishment of local transmission. However, in an area where the transmission is already established, weekly reporting of cases is enough.

2. Laboratory diagnosis confirmation

Diagnostic protocol

The recommended protocol for confirmation of cases is to use RT-PCR on serum from day one to five after the onset of symptoms, in addition to serological assays for IgM detection from day six onwards. Confirmatory assays are required in the case of a primary alert. Results from RT-PCR can be obtained within 48 hours. Cases with negative PCR within five days of the onset of symptoms, or with negative serology as from the sixth day, can be considered 'non-cases' and thus be excluded from further case reports.

Regarding serology testing, there are few commercial immuno-fluorescence assays (IFA) available, such as EUROIMMUN AG (Lübeck, Germany). This assay was validated by the European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD). Since an IFA test allows only a limited number of blood samples to be analysed at the same time, the development of an ELISA test is needed to ensure analysis of larger quantities of samples, e.g. in the event of large outbreaks or serosurveys.

Diagnostic capacity

In the event of an outbreak, Member States should be prepared to deal with an increased demand for testing. Development of diagnostic capacity and regular quality control needs to be organised by the reference laboratory to ensure reliable test results.

In the existence of local diagnostic capacity, regular communication between the regional and national laboratory and epidemiological surveillance level is needed to ensure consistent data collection and management, as well as further investigation of negative cases (e.g. dengue cases could also fall under the case definition). As indicated above, a common web-based database providing access for the different partners could be considered.

Priority for laboratory analysis

Special attention should be given to the timeliness of test results, in particular when the implementation of vector control measures is based on the presence of confirmed cases (see Annex 3.4). When confronted with large number of requests for testing, laboratories should give priority to:

- suspected cases from new areas, where *Aedes albopictus* is present, and where no transmission is known to be established;
- cases with the most recent date of onset of symptoms.

3. Professional and public awareness-raising

As soon as foci of local virus transmission are identified, it is important to raise the awareness among healthcare providers on the ongoing epidemic, for them to be familiar with the case definition (including the algorithm) and the diagnostic procedures, in order to ensure a rapid detection of new cases.

At the same time, information and education of the general public will increase awareness about the possibility of the disease, and the need to seek medical advice if symptoms appear (fever with incapacitating arthralgia).

In areas where virus transmission has occurred in the past, or where the risk for establishment of transmission is high, it is useful to launch general information campaigns at the beginning of spring, when vector activity is known to start. Such campaigns are aimed both at the healthcare professionals, for them to include chikungunya in the differential diagnosis, as well as at the general public, to be aware about the mosquito as a vector for disease, and the importance of reducing mosquito breeding sites.

Finally, advice should be given to people visiting areas with Chikungunya virus transmission on how to avoid mosquito bites, and to those returning from such areas, in order to ensure rapid detection of cases (see Annex 7).

4. Vector control and monitoring

Vector control

In areas where local virus transmission is ongoing, the rapid implementation of vector control measures is essential to limit the risk for further spread of transmission. The priority for such control measures lies in the collaboration of the community in the control of mosquito breeding sites. Education of the general public on the possible breeding sites and how to eliminate those, in a locally adapted way, should be considered as the basis for efficient vector control. Such education campaigns should be maintained during the whole period of vector activity.

In addition to the control of the breeding sites, larvicides and adulticides are used around each identified case (100m radius) or around each identified cluster of cases (300m radius). Often, this is contracted out to private companies. Precise terms of reference including quality control monitoring of these disinfestation activities are essential to ensure an optimal implementation of the control measures, in order to achieve the best impact possible.

In areas where the vector is present, these vector control measures need to be implemented *immediately* for all confirmed and probable cases. As for the possible cases, not having visited or resided in an area of transmission, the measures are implemented only upon their laboratory confirmation. The rationale for not implementing the vector control measures immediately for possible cases is based on the fact that the chikungunya diagnosis, even though clinically compatible, is unlikely in the absence of travel or residence in an area where transmission of chikungunya is present, and the positive predictive value of the diagnostic tests will decrease.

Vector monitoring

In areas where *Aedes albopictus* is known to be present, vector monitoring activities should be established or strengthened. Although there is no information available on a threshold for mosquito density which would allow Chikungunya virus transmission, knowledge on the level of vector activity is a key determinant for the risk of the establishment of transmission. In addition, linking the surveillance data to weather forecast data may enable an estimate of the likely start of the hatching of the mosquito eggs in the spring, and hence the start of the season of vector activity.

In areas where Chikungunya virus transmission has occurred, it will be important to further investigate and monitor the parameters that influence the likelihood for re-emergence of the virus in the spring of following year(s) (such as the activity of adult mosquitoes during the winter period, and the occurrence of vertical virus transmission in *Aedes albopictus*) and implement measures to limit (if possible) the likelihood of re-emergence of infected mosquitoes next spring.

In areas where there is no information available on the presence of *Aedes albopictus*, but where environmental and ecological conditions are favourable for its introduction, a vector monitoring system allows the early detection of its introduction. This is important for the rapid implementation of vector control measures around the site of introduction, in order to limit the risk for the establishment of *Aedes albopictus* in the area.

5. Blood transfusion

Chikungunya virus can be transmitted through blood transfusion and organ donation; the risk for transmission is linked to the disease incidence. Whether an area is considered high or low incidence needs to be determined based on a quantitative risk assessment.

Persons living in high incidence areas of established virus transmission should be excluded from blood donation as long as transmission is ongoing.

In low incidence areas, the strategy will depend on the local situation. If possible, all persons from the area (e.g. the 4th administrative level, considering the country level as the first) could be excluded from blood donation. In case the consequences of such decrease in donations are not acceptable, an alternative solution needs to be considered, based on the quantification of the risk, which is influenced by the proportion of asymptomatic cases (estimated at 6% in La Réunion, 25% in Mayotte) and the period of viraemia before the onset of symptoms (estimated to be 24–48 hours). For example, quarantining the donated blood for 48 hours, after which the clinical evaluation of the donor is repeated, would substantially reduce the risk for transmission of the virus. However, such strategies can only be applied with confidence when a well-functioning and reliable case detection, confirmation and reporting system is in place.

The availability of a rapid diagnostic test for chikungunya would be very valuable for further narrowing down the number of excluded donors. However, the feasibility of developing such a test needs to be assessed.

6. Research

To continue improving and broadening the knowledge on chikungunya infection, transmission and control, the virus, the vector and the dynamics of the epidemics, each opportunity for operational research needs to be optimally used.

With regards to the field of public health, the focus of research could include the assessment of the extent of spread in the affected area, assessment of risk factors for infection and the proportion of asymptomatic infection, the estimation of the Basic Reproduction Number (R_0) through modelling, the estimation of the risk for reintroduction of the virus through international travel, the assessment of knowledge, attitude and practices related to the disease, etc.

Further research would be useful on the clinical management of cases, what would be the best treatment in general, and of severe cases in particular, what are the mid- and long-term consequences for patients, including their quality of life, what are the possibilities for the development of diagnostic and screening tests (cf. importance for blood or organ transplantation), for the development of treatment and vaccine, etc.

More knowledge on the virus is also required, in terms of the characterisation and sequencing of the virus causing a specific outbreak, the determination of the interaction between the host and the mosquitoes, the existence of a reservoir in mammals, etc.

As for the vector, questions remain with regards to the optimal environmental and ecological conditions for its development, what are the most suitable indexes for monitoring vector density, could a threshold of vector density or vector activity be identified and monitored to indicate an epidemic risk for chikungunya, the further determination of the vector competence, documentation of vertical transmission of the virus through field studies, etc. In addition, further assessment of the impact of current vector control strategies around cases is needed since these are still more empirical than based on evidence of an epidemiological impact. The impact of the short- and long-term use of insecticides on the population and the environment would also need to be documented.

This list is not exhaustive, but the documentation of the lessons learnt from the response to the current outbreak, will be useful for improving the response to future outbreaks.

ANNEX 4. CHIKUNGUNYA CASE DEFINITION FOR SURVEILLANCE

The definition uses:

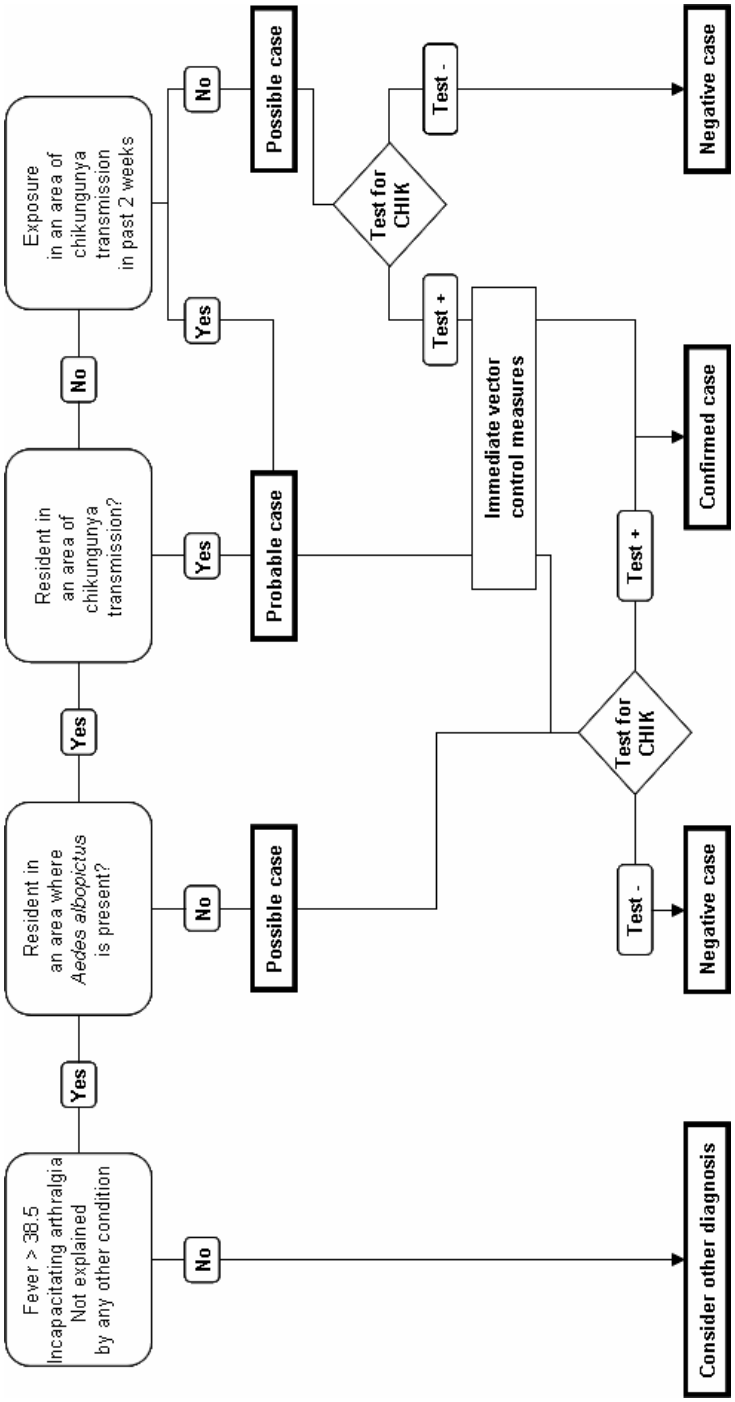
- **Clinical criteria**: acute onset of fever >38.5°C and severe arthralgia not explained by other medical conditions.
- **Epidemiological criteria**: residing or having visited epidemic areas, having reported transmission[3] within 15 days prior to the onset of symptoms.
- **Laboratory criteria**: at least one of the following tests in the acute phase:
  - virus isolation;
  - presence of viral RNA by RT-PCR;
  - presence of virus specific IgM antibodies in single serum sample collected;
  - seroconversion to virus-specific antibodies in samples collected at least one to three weeks apart;

On this basis, the following categories of cases are reported:

- **Possible case**: a patient meeting clinical criteria.
- **Probable case**: a patient meeting both the clinical and epidemiological criteria.
- **Confirmed case**: a patient meeting the laboratory criteria, irrespective of the clinical presentation.

[3] Areas of local transmission are defined as the 4th administrative level (considering the country level as the first) in which two or more chikungunya cases were identified with no epidemiological link.

ANNEX 5. ALGORITHM FOR ASCERTAINMENT OF SUSPECTED CHIKUNGUNYA CASE



ANNEX 6. SUGGESTED SURVEILLANCE FORMS FOR REPORTING ON EUROPEAN LEVEL

Chikungunya individual case reporting line listing

REPORTING OFFICER

Date of report / / Case code by reporter

Name Tel. No (+country code + number)

Institution/organization Country

REPORTING PLACE AND PERIOD

Report for country

2nd administrative level (region) 3rd administrative level (province) 4th administrative level (municipality)

Report for period from / / to / /

CASE INFORMATION

Sex (M/F)	Age in years	Region, province and municipality of residence	Onset date	Region, province and municipality of exposure

Please, send the filled form by email to ezo@ecdc.europa.eu OR by fax +46 8 586 01 001. Thank you!

For ECDC use only ID num Form validated ☐ Form entered ☐

Chikungunya aggregated case reporting form

REPORTING OFFICER

Date of report / / Case code by reporter

Name Tel. No (+country code + number)

Institution/organization Country

REPORTING PLACE AND PERIOD

Report for country 2nd administrative level (region)

3rd administrative level (province)

4th administrative level (municipality)

Report for period from / / to / /

REPORT

Number of new confirmed cases during reporting period (laboratory confirmed)

Number of new confirmed cases during reporting period with epidemiological link to a known area of transmission

Please, send the filled form by email to ezo@ecdc.europa.eu OR by fax +46 8 586 01 001. Thank you!

For ECDC use only

ID num Form validated ☐ Form entered ☐

ANNEX 7. RECOMMENDATIONS FOR TRAVELLERS

Recommendations to visitors to areas with chikungunya transmission

Visitors to any area where there is transmission of Chikungunya virus are advised to take the following preventive measures to minimise the exposure to mosquito bites while there.

Use anti-mosquito devices (insecticide-treated bed nets, spray, repellents, etc.) and wear long-sleeved and long-legged clothes, especially during the hours of highest mosquito activity.

Mosquito repellent based on a 30% DEET concentration is recommended. Before using repellents, pregnant women and children under the age of 12 years should consult a physician or pharmacist. For newborn children under three months, repellents are not recommended; instead, insecticide-treated bed nets and protective clothing should be used.

Pregnant women, immuno-deprived people and people suffering from a severe chronic illness should consult their physicians prior to travel in order to assess the risk and get recommendations on personal preventive measures.

Recommendations for those who return from the area

People who have visited any area where Chikungunya virus transmission occurs, and who develop a high fever along with unexplained joint pain in the 12 days after their return are advised to seek medical attention. It is especially important for them to take preventive measures to reduce mosquito bites while symptomatic in order to avoid possible further mosquito transmission to others (with appropriate protective clothing, use of repellent and anti-mosquito devices such as insecticide-treated bed nets, spray, repellents, etc, as explained above).