RAPID RISK ASSESSMENT

Multiple reports of locally-acquired malaria infections in the EU

20 September 2017

Main conclusions and options for response

Five events of local malaria transmission have been reported recently in the EU. Three of these events were associated with either mosquito-borne transmission from an imported case (introduced malaria) or an imported infected mosquito (airport malaria), in Greece and northern Cyprus (*P. vivax*), and in France (*P. falciparum*); and two of the cases were most likely associated with nosocomial mosquito-borne or iatrogenic transmission of *P. falciparum,* in Italy and Greece.

The following options should be considered for preventing and controlling mosquito-borne transmission of malaria:

- increasing awareness of risk and bite avoidance for travellers and residents in EU areas where introduced malaria has been reported;
- increasing awareness among clinicians surrounding the sporadic occurrence of locally-acquired malaria cases in the EU;
- consideration of malaria infection by health practitioners in the EU/EEA Member States in the differential diagnosis for symptomatic persons returning from affected areas in countries with recently recorded local mosquito-borne malaria transmission;
- rapid notification of cases to ensure the timely implementation of appropriate public health measures in areas with competent vector populations;
- implementation by EU Member States of safety measures defined in the EU Directives 2006/17/EC and 2004/33/EC [1,2] and the technical guide to the quality and safety of organs for transplantation [3]. EU Member States with locally transmitted infections may apply blood safety measures as suggested in the ECDC expert opinion [4]. EU Member States may decide whether to implement preventive measures for persons returning from the affected areas in non-endemic countries, taking into account the measures currently being implemented by the local blood safety authorities.

Healthcare providers should be aware of the risk of nosocomial transmission of malaria and enforce standard precautions to prevent this. The risk of further spread of malaria in the EU associated with these events is considered very low.

Erratum 25 September 2017: page 3 - indigenous malaria was corrected to malaria infection, page 6 – the following sentence was changed to, 'locally-acquired cases showed evidence of the presence of *Anopheles maculipennis s.l.* (under investigation for species identification) and *Anopheles claviger s.s.* but did not detect the presence of *Anopheles plumbeus*.'

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The following options should be considered for preventing nosocomial transmission of malaria:

- strict application of standard precautions in healthcare settings for patients presenting with malaria;
- application of measures to prevent vector-borne transmission around hospitalised cases of malaria while parasitaemic, such as mosquito-nets, the use of repellents or insecticides in areas with competent, active vector populations;
- the triggering of an immediate investigation of infection control practices related to blood-borne transmission when a nosocomial transmission of malaria is suspected.

Source and date of request

ECDC internal decision, 11 September 2017.

Public health issue

In the context of five recent events of local malaria transmission in the EU, we assess the risk of malaria spread in the EU.

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All experts have submitted declarations of interest and a review of these declarations did not reveal any conflict of interest.

Experts from WHO reviewed this risk assessment, however the views expressed in this document do not necessarily represent the views of WHO.

Disease background information

Malaria is caused by *Plasmodium* parasites transmitted by the bites of infected females of various *Anopheles* mosquito species. Among *Plasmodium* parasites, *P. falciparum* can lead to life-threatening infection and is the most prevalent malaria parasite on the African continent. In addition, *P. vivax* infection can lead to malaria relapses and commonly infects humans in many countries outside of sub-Saharan Africa. All EU Member States are considered free of *P. falciparum* and *P. vivax* malaria. More information about malaria is available in the ECDC malaria factsheet.

Surveillance of malaria in the EU

Malaria is a notifiable disease in the EU. The EU case definition requires the presence of fever or a history of fever, and the presence of parasites detected in a blood film or the detection of *Plasmodium* nucleic acid or *Plasmodium* antigens in blood.

In the EU/EEA countries, 31 966 cases of malaria were reported between 2012 and 2016, corresponding to an annual average of around 6 400 cases (range: 5 272 cases in 2012 to 7 147 cases in 2016). In 99.8% of the cases infection occurred in malaria-endemic countries. The notification rate increased from 0.8 per 100 000 population in 2012–2013 to 1.0 per 100 000 population in 2014–2016.

In 2016, 10 cases were reported to ECDC as locally acquired: six cases in Greece, two in France, and one each in Spain and Lithuania. These cases are considered sporadic and result from transmission by a local mosquito infected from an imported case (introduced malaria) or by an infected mosquito that was transported by aircraft from a malaria-endemic country (airport malaria). No sustainable locally-acquired transmission of malaria was reported in the EU/EEA in 2016.

Between 2009 and 2017, the Hellenic Centre for Disease Control and Prevention recorded 95 locally acquired *P. vivax* malaria cases resulting from an introduction in an area with a competent vector population: 76 cases between 2009 and 2013, none in 2014, eight in 2015, six in 2016 and five in 2017 (as of 17 August 2017). Following a peak in local malaria transmission during the period 2011–2012 in Greece, the number of locally-acquired malaria cases declined steadily in the subsequent years, with only sporadically introduced cases being reported. This coincided with the implementation of intense public health intervention measures, in cooperation with various stakeholders at the national, regional and local level, which successfully prevented the re-establishment of malaria in Greece [5,6].

Modes of transmission of malaria

For epidemiological surveillance, malaria cases are classified as imported if the transmission of the parasite occurred outside of the EU, or indigenous if the transmission of the parasite occurred within the EU. In addition, *Plasmodium vivax* and *Plasmodium ovale* may cause relapses of malaria several months or years after the initial transmission event and the first episode of malaria.

Malaria infection may result from different modes of transmission:

- Airport malaria or suitcase malaria: the transmission results from the bite of an infected mosquito imported into the EU in an aircraft [7]. Airport malaria remains a rare event with limited numbers of cases being reported in recent years.
- Introduced malaria: the transmission results from the bite of a local mosquito infected by an imported case. In the EU/EEA countries, several areas have experienced introduced malaria: Greece since 2009 [6,8-10]; France (Corsica) in 2006 [11] and Spain in 2010 [12].
- Induced malaria: the transmission results from the introduction of the parasite into a person by artificial means, usually of iatrogenic origin, including blood transfusion, organ transplant, or the shared use of needles or syringes contaminated with blood. Malaria may also be transmitted from a mother to her unborn infant before or during delivery. Induced malaria cases have been reported occasionally in the EU.

WHO defines a malaria focus as follows [13,14]:

- An active focus is an area where indigenous case(s) have been detected within the current calendar year.
- A residual non-active focus is an area where no indigenous transmission has occurred within the past three years.
- A cleared-up focus is an area with no indigenous transmission for more than three years.

Although uncommon, nosocomial transmission of *P. falciparum* malaria, vector-borne or iatrogenic, has been previously documented. In most instances, transmission occurs from an admitted, imported patient to other patients in the same ward whereby molecular analysis finds the parasite strains to be similar but vector-borne transmission is considered unlikely by the investigators. Although transmission has been associated with needle-stick injuries [15], incorrect capillary blood sampling techniques for blood-glucose measurement [16] and contaminated gloves [17], the mode of transmission remained unestablished in the majority of cases [18-20]. When investigations rule out transfusion and needle-stick injury, the most common hypothesised mode of transmission for healthcare-associated *P. falciparum* infections remains an unidentified breach in infection control. In Germany in 2016, a patient who had shared a room with a malaria case in a hospital ward for under 24 hours subsequently developed malaria. Malaria strains for both patients showed identical DNA patterns. Vector transmission was ruled out as transmission took place during the winter. The mode of nosocomial transmission was not elucidated [21]. In Italy, a nosocomial transmission of malaria was ascertained to probably be due to patient-to-patient transmission via a contaminated blood glucose metre [16]. Several additional cases of suspected nosocomial transmission have been reported [22Velasco, 2017 #454,23].

Malaria parasites may be transmitted through substances of human origin (SoHO) when a donor is an asymptomatic carrier of *Plasmodium* spp. [24-26]. In addition, most available malaria screening tests, including nucleic acid testing (NAT), have limited sensitivity to very low levels of parasites in blood sufficient to transmit malaria. To date, there is no evidence-based guidance for malaria screening methods in connection with blood donation in malaria-endemic areas. In non-endemic countries, the application of blood safety measures has been successful in keeping the incidence of transfusion-transmitted malaria low, and the rejection rate of donors for malaria risk in various countries has been estimated to be 0.003–0.43% of all donations [27]. Similar safety measures to those applied to donors of cells, tissues and organs may also effectively reduce the unnecessary deferral of donors but cannot be completely exclude the possibility of malaria transmission through donations from asymptomatic carriers of *Plasmodium* spp. The highest risk of malaria transmission is through contaminated erythrocyte-containing blood components and peripheral blood stem cells. Transmission has also been reported through kidney, liver and heart transplantation, as well as through cortical bone, cornea, and epidermis.

Blood safety measures for malaria

Blood safety measures depend on whether the area where blood or tissue donation is taking place has known ongoing malaria transmission events. In non-endemic areas or countries, according to EU Directive 2004/33/EC, individuals with a history of malaria should be temporarily deferred from blood donation for three years following cessation of treatment if they are asymptomatic and an immunological or molecular genomic test is negative [2]. The directive also specifies deferral periods and/or laboratory screening for individuals who have lived in an endemic area within the first five years of life, for asymptomatic visitors returning from malaria endemic areas or for individuals with a history of undiagnosed febrile illness during or within six months of a visit to an endemic area.

In the event of a case of locally transmitted malaria in non-endemic countries, blood safety measures could be applied to an administrative geographic unit covering an area with a 2–6 km radius around the places of reported transmission(s), taking into account the geomorphology of the area [4]. Measures comprise identification of donors at risk; the deferral of donors and/or cessation of collection activities in the affected areas or the laboratory screening of donations; reinforcing post-donation information, and pathogen inactivation of whole blood or all blood components if possible. The measures should continue until the end of the mosquito season even if there are no new cases reported. At this point, measures may be stopped, although, given that incubation periods are related to season length, the laboratory screening of donated blood should continue at least until the start of the next season of mosquito activity [4]. Based on a risk assessment, EU Member States may decide whether to implement preventive measures for persons returning from the affected areas in non-endemic countries, taking into account the measures currently being implemented by the local blood safety authorities.

Cells and tissues from potential deceased donors should be rejected if there is evidence of the risk factors for malaria based on the risk assessment, taking into consideration travel and exposure history and local malaria prevalence. For living donors of cells and tissues, laboratory testing may be required, depending on the donor's history and the characteristics of the tissues and cells donated [1].

Organ donors at risk of malaria infection should be laboratory tested. Parasitaemic donors are usually rejected by transplant centres. Organs from donors who have been successfully treated and recovered from malaria may be used with some exceptions – e.g. liver donation. Prophylactic treatment of recipients may also be considered. It is recommended that a transplant and malaria/tropical medicine specialist should be consulted [3].

Competent mosquito vectors in the EU

Several *Anopheles* mosquito species competent for malaria transmission are present in Europe. In south-western Europe, *Anopheles atroparvus* is the historical vector of *P. falciparum* and *P. vivax* [28]. However, the species is refractory to tropical strains of *P. falciparum*.

In central and eastern Europe, *Anopheles messeae* and *Anopheles maculipennis s.s.* are historical vectors of *P. vivax* [28,29]. Other possible vectors are *Anopheles claviger* for *P. vivax* and *Anopheles plumbeus* for *P. falciparum*. Both species are generally scarce but *Anopheles plumbeus* can be found in high densities in some places, such as around inoperative farms. *Anopheles plumbeus* presents moderate-to-high receptivity for *P. falciparum* in laboratory conditions [30].

In the Mediterranean region, *Anopheles atroparvus* can act as a malaria vector in the Iberian Peninsula. *Anopheles labranchiae* and *Anopheles superpictus* can act as malaria vectors in parts of Italy. *Anopheles labranchiae* can act as a malaria vector in Corsica whereas *Anopheles sacharovi* can act as a malaria vector in the Balkans [31]. In the Peloponnese region of Greece, *Anopheles maculipennis s.s.*, *Anopheles sacharovi*, *Anopheles hyrcanus* and *Anopheles superpictus* have been identified as competent vectors [31]. Throughout eastern Greece, *Anopheles sacharovi* and *Anopheles superpictus* have been implicated as the probable dominant vectors [8,32]. In Cyprus, the competent vectors *Anopheles claviger* and to a lesser extent *Anopheles algeriensis*, *Anopheles sacharovi* and *Anopheles superpictus* are present [33].

Event background information

Since May 2017, France, Italy, Greece and the United Kingdom have reported malaria cases infected within the EU, as set out in the table below.

Table 1. Number of cases of locally acquired malaria in the EU, by country of report, May-September 2017

Country of report	No.	*Plasmodium* species	Date of onset	Suspected mode of transmission, place of infection	Date of report
France	2	*P. falciparum*	26 August	Mosquito-borne, Allier, France.	7 September
Greece	5	*P. vivax*	2 May–22 July	Mosquito-borne, regions of Dytiki Ellada and Sterea Ellada, Greece.	18 May, 21 July, 17 August
	1	*P. falciparum*	17–23 July	Mosquito-borne or nosocomial, region of Ipeiros, Greece.	17 August
Italy	1	*P. falciparum*	29 August	Mosquito-borne or nosocomial, Trento l, Italy.	5 September
United Kingdom	3	*P. vivax*	29 August	Mosquito-borne, the northern part of Cyprus.	8 September

Italy

On 5 September, Italy reported a fatal case of malaria in a four-year-old girl with no travel history to a malaria-endemic country [34]. She was admitted to a hospital in the Veneto region on 13 August 2017 and diagnosed with diabetes mellitus. After returning from the Veneto region, she was admitted to a Trento hospital for her diabetes from 16 to 21 August and diagnosed with pharyngitis on 31 August 2017.

On 2 September 2017, she was admitted and diagnosed with *P. falciparum* malaria and subsequently transferred to the tropical diseases reference centre in Brescia where she died on 4 September 2017. Epidemiological investigations identified two patients infected with *P. falciparum* who were hospitalised in the same ward during her stay in the Trento hospital from 16 to 21 August. The investigation at the Trento hospital did not identify breaches in medical procedures that could have resulted in an iatrogenic transmission.

Entomological investigations in the area of Trento did not reveal the presence of *Anopheles* mosquitoes. Entomological surveys in Bibione, where the girl spent her holidays, are ongoing. Molecular sequencing of the *Plasmodium* strain from the girl and the other two children hospitalised concomitantly is being carried out to assess the link between the cases.

Greece

As of 17 August 2017, Greece had reported five locally-acquired cases of *P. vivax* malaria acquired via vector-borne transmission. Four of the cases were likely to have been exposed in the region of Dytiki Ellada in western Greece and one case was likely to have been exposed in Sterea Ellada in central Greece [6]. Greece considers these cases as introduced, resulting from a first-generation local transmission following a recent introduction of *P. vivax* into the area. The dates of onset for the cases ranges from 2 May to 22 July 2017.

In addition, Greece reported one locally acquired case of *P. falciparum* in the region of Ipeiros, in the north-west of Greece with date of symptom onset between 17 and 23 July 2017. The case, who has no recent travel history to a malaria-endemic area, was recently hospitalised in a ward where a patient was treated for *P. falciparum* malaria. The date of symptom onset is compatible with a vector-borne transmission through a mosquito infected in the ward. The investigation concluded that the case could be the result of either a nosocomial vector-borne transmission or a nosocomial transmission of iatrogenic origin, but was not related to blood transfusion. Response measures were promptly implemented for both possible modes of transmission. Entomological investigations in the area did not reveal the presence of *Anopheles* mosquitoes. However, this targeted investigation could not rule out the previous or current presence of *Anopheles* mosquitoes in the area. No further locally-acquired malaria cases have been reported in the area despite the increased awareness among local clinicians.

United Kingdom ex. the northern part of Cyprus

On 8 September 2017, the United Kingdom reported three cases of *P. vivax* malaria in travellers returning from Esentepe, the northern part of Cyprus, through the Early Warning and Response System (EWRS). Two of the cases were 12-year-old siblings that travelled independently from the third case. The three cases stayed in the northern part of Cyprus for two to three weeks in August and developed symptoms on 29 August 2017. The cases were laboratory-confirmed upon returning to the UK.

France

On 7 September 2017, France reported two locally- acquired cases of malaria. Both cases attended a wedding that took place between 11 and 16 August 2017 in Moulins, in the Auvergne-Rhône-Alpes region of France. On 30 August 2017, the first case was hospitalised in south-west France after four days of fever, chills and sweats and was found positive for *P. falciparum* malaria. The patient had not travelled abroad and had no risk factors for induced malaria. The only recent travel identified was to Moulins and its surrounding area to attend the wedding. On 1 September 2017, a second case who attended the same wedding was diagnosed upon return to his home country outside the European Union. The case had onset of symptoms on 26 August 2017 and had neither exposure to induced malaria nor recent travel history to a malaria-endemic area.

None of the wedding attendees reported a recent travel history to a malaria-endemic country or symptoms compatible with malaria. The regional health agency of Auvergne-Rhône-Alpes carried out active case-finding in local laboratories and hospitals. A case of *P. falciparum* malaria imported from Burkina Faso was identified in an individual who stayed in Moulins and its surroundings for several days within the two weeks prior to the wedding.

Entomological investigations conducted on 5–7 September in the area visited by the imported and locally-acquired cases showed evidence of the presence of *Anopheles maculipennis s.l.* (under investigation for species identification) and *Anopheles claviger s.s.* but did not detect the presence of *Anopheles plumbeus*. Human landing catches revealed that these mosquitoes are not aggressive towards humans and are probably zoophilic in this area where there are many cows and horses. The French National Reference Centre for malaria is gathering samples for molecular typing to assess the link between the imported and the two locally-acquired cases.

ECDC threat assessment for the EU

Four EU Member States have reported the occurrence of malaria cases due to *P. falciparum* and *P. vivax* acquired in the EU. Greece has reported local transmission of *P. vivax* since May 2017 while other transmission events occurred in July 2017. The risk of malaria spread in the EU following these events remains very low.

P. falciparum transmission events

Greece and Italy

Two events involving nosocomial transmission of *P. falciparum* took place in Italy and in Greece. In both cases, the investigation was not conclusive, as breaches in infection control that could have resulted in a iatrogenic transmission were not identified and *P. falciparum* competent vectors were not identified as a result of entomological investigations. Laboratory investigations are ongoing and may provide additional insights into the link between cases and the origin of the strains.

Although transmission to further individuals may have occurred at the time of the events, it is unlikely that this would have been extensive and the risk of further malaria spread in these nosocomial contexts is very low. However, the two events suggest that nosocomial malaria transmission is possible if preventive measures for mosquito transmission or iatrogenic transmission are not strictly applied.

France

The epidemiological investigation identified the presence of a case *P. falciparum* malaria in the same area prior to the exposure period for the two reported cases. Both cases shared an epidemiological link with the imported malaria case in that they stayed in and around the city while attending the wedding event, which may have resulted in a local mosquito-borne transmission. Entomological investigations did not identify mosquito-vectors that could support the hypothesis of a vector-borne transmission by a competent local anopheline mosquito. A cluster of two airport malaria cases therefore remains a possible hypothesis. Molecular typing of the strains should provide further evidence.

While a few additional cases may have been infected at the time of the event in France, the risk of further malaria spread in this area is very low.

P. vivax transmission events

Greece

Since 2009, Greece has been detecting locally acquired cases of *P. vivax* malaria almost every year following re-introduction into receptive areas (i.e. areas with active and competent malaria anopheline vectors). Therefore, the reporting of introduced cases is not unexpected in specific, vulnerable and receptive areas. The locations involved were considered to be receptive and vulnerable areas [8,35]. In 2011, ECDC published a rapid risk assessment on the situation in Greece and reports on successive missions to Greece in 2011 and 2012 [9,10,36].

Epidemiological and entomological investigations in Greece support the hypothesis of recurrent introductions of *Plasmodium vivax* into receptive areas (i.e. areas with active and competent malaria anopheline vectors). As the 2017 mosquito season has not yet come to an end, the reporting of additional sporadic introduced cases of *P. vivax* malaria cannot be excluded. However, the risk of *P. vivax* infection for residents and travellers in the areas where malaria has been introduced is very low.

The northern part of Cyprus

This is the first time that cases of malaria acquired in the northern part of Cyprus have been reported among EU travellers in recent years. Receptive areas are likely to exist on the island of Cyprus due to its Mediterranean climate, the presence of competent vectors for *P. vivax* and historical transmission of malaria prior to 1945. The occurrence of travel-associated cases is unusual and it is presumed that local transmission occurred in the area where the cases stayed in the northern part of Cyprus. Suitable climatic conditions and the presence of competent mosquito vectors for *P. vivax* in certain areas of Cyprus make the local transmission of *P. vivax* possible around an imported case (introduced malaria). However, airport malaria cannot be ruled-out as tourists from malaria-endemic countries are likely to have visited the island.

Further similar events may occur in Greece and in Cyprus until the climatic conditions are no longer favourable for the activity of the mosquito vectors. Similar events have been seen in the past in Italy and Spain [12,37]. Therefore, similar malaria introductions may also occur in other receptive areas in the south of the EU where competent vectors are present and climatic conditions are favourable for their activity. No changes in species distribution or the abundance of anopheline mosquitoes have been observed in recent years in the EU/EEA.

Through the VectorNet project, ECDC and the European Food Safety Authority (EFSA) are monitoring the distribution of malaria-competent vectors in the EU and neighbouring countries to assess the risk of malaria transmission within the EU [38].

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