RAPID RISK ASSESSMENT

Outbreak of plague in Madagascar, 2017

9 October 2017

Main conclusions and options for response

Since 23 August 2017 Madagascar has been experiencing an outbreak of plague, and as of 3 October 2017, 194 cases and 30 deaths (case fatality rate 15.5%) have been reported. Of these cases, 124 cases are pneumonic plague including 21 deaths, 68 are bubonic plague, including nine deaths, one is a septicemic plague and one is an undetermined plague case. The cases are from 20 central, eastern and northern districts in Madagascar.

While plague outbreaks in Madagascar are not unexpected, the high proportion of pneumonic plague is of concern. The risk of further transmission in Madagascar is considered high until public health prevention and control measures are fully implemented with the support of the World Health Organization (WHO) and international partners. The risk of regional spread in the Indian Ocean region is considered moderate.

The risk for travellers from the EU or for importation to the EU is considered very low. However, Member States should consider reviewing their preparedness plans for imported cases. WHO considers the risk for international spread of plague to be very low and advises against any restrictions to travel and trade with Madagascar based on the information to date. There is no restriction of movement in and out of Antananarivo, where cases have occurred, in accordance with the recommendations of the Malagasy authorities.

According to WHO, prophylactic treatment is only recommended for persons who have been in close contact with plague cases, or who have experienced other high-risk exposures such as bites from fleas or direct contact with bodily fluids or tissues of infected animals.

The preventive measures for travellers to endemic plague areas include:

- use of personal protection against fleabites. As Madagascar is a malaria endemic area, the use of mosquito repellents for malaria prevention can protect against flea bites
- avoidance of direct contact with sick or dead animals
- avoidance of close contact with sick persons and in particular with patients diagnosed with pneumonic plague or patients with symptoms consistent with pneumonic plague
- avoidance of crowded areas where cases of pneumonic plague have been recently reported
- contacting travel clinics before departure to get information about the current plague outbreak in Madagascar including preventive measures and symptoms of pneumonic plague
- seeking immediate medical care if compatible symptoms are developed.

If travellers returning from Madagascar present with suggestive symptoms (fever, painful lymphadenopathy) they should inform their healthcare provider of their travel to Madagascar. They should also be investigated for possible exposure to animal or rodent vectors within the preceding 10 days and tested for plague in case of suspicion.

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Erratum (10 November 2017): on p 3 (Plague in Madagascar) the figure of 200 cases of bubonic plague annually was incorrect and this has been amended to 400 cases annually.

Source and date of request

WHO International Health Regulation message, 26 September 2017 and ECDC internal decision, 2 October 2017.

Public health issues

To assess:

- the likelihood of spread and the public health impact of the outbreak of plague in Madagascar
- the likelihood of spread to neighbouring countries, including the EU Outermost Regions (OMR) and Overseas Countries and Territories (OCT)
- the risk for EU citizens residing in or travelling to the affected areas in Madagascar.

Consulted experts

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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

Plague is a bacterial zoonotic disease caused by the Gram-negative bacillus *Yersinia pestis*. Plague is predominantly a zoonosis of rodents. The transmission among rodents or from rodents to humans occurs through flea bites. Other mammals, domestic or wild, can also be infected. Humans are described as incidental hosts, not contributing to the natural enzootic disease cycle [1,2].

Between 2010 and 2015, plague cases were reported in several parts of the world including in Africa (Democratic Republic of Congo, Madagascar, Uganda and United Republic of Tanzania), Asia (China, Russian Federation, Kyrgyzstan and Mongolia) and the Americas (Bolivia, Peru and the United States of America) [3]. The Democratic Republic of Congo and Madagascar reported 92% of the number of cases from 2010 to 2015 period [3].

Human infections occur most frequently in and around households during an epizootic in the murine population ecologically associated with humans [4]. *Yersinia pestis* is often transmitted through the bite of infected fleas, but human-to-human infection can also occur through droplet transmission from a pneumonic plague case.

There are three main transmission routes of plague to humans:

- Vector-borne: transmission between rodents occurs through bites from infected fleas, and this is also the most common way in which humans are infected, leading to the bubonic plague. The rodent flea is usually involved in the transmission of *Y. pestis* from plague–infected rodents to humans. Human ectoparasites such human fleas (*Pulex irritans*) and body lice were proposed as an alternative model of transmission for historical plague pandemics [5,6].
- Direct contact: handling of an infected animal can also result in human infection. *Y. pestis* can enter the human organism through bites from an infected animal or through contact with infected tissues with scratches, skin lesions or the mucous membranes of the mouth, nose or eyes. Eating infected animals can also lead to infection.
- Droplet: mainly human-to-human transmission from pneumonic plague cases via bacteria-containing droplets, during close face-to-face contact, in particular during the late stage of the infection [4].

Plague occurs in three main clinical forms:

- The bubonic plague is the most common form (80 to 95% of cases) and results from the infection of the lymph nodes draining the inoculation site of the bacillus. After an incubation period of one to seven days, patients develop sudden onset of fever, with headache, chills, weakness and intense pain and swelling in a lymph node related to the area of inoculation. The latter lesion, named bubo, corresponds to a painful enlarged lymph node usually localised in the inguinal, axillary or cervical region. Untreated bubonic plague has a fatality rate of 50% to 60% which decreases to 10% to 20% with early antibiotic treatment [4]. It is not transmitted from one person to another unless there is direct contact with pus from the suppurated buboes.

- The second form, the septicemic plague, is due to the dissemination of the infection in the bloodstream. Septicemic plague can occur as the first symptom of plague or may develop from untreated bubonic plague. In the absence of distinctive clinical clues, such as a bubo, the septicemic form of plague may be challenging to diagnose in a timely manner. Patients develop fever, chills, extreme weakness, and gastro-intestinal symptoms which are followed in the later stages of the disease by disseminated intravascular coagulation and multi-organ failure.
- The third clinical form, the pneumonic plague, can result from direct infection of the airway system (primary pneumonic plague) or more commonly, from bacterial seeding to the lungs as a result of haematogenous diffusion (secondary pneumonic plague). The incubation period is very short ranging from one to four days and possibly even less than 24 hours [4]. Patients develop fever, headache, weakness, and a rapidly developing severe pneumonia with shortness of breath, chest pain, cough and sometimes bloody or watery mucous. The pneumonic plague causes severe pneumonia with respiratory failure and shock. Untreated pneumonic plague is fatal. Human-to-human transmission of plague via contaminated droplets during very close contact has the potential of propagating the epidemic [4].

Definitive diagnosis for plague is made through the isolation and identification of *Y. pestis* in clinical specimens or a diagnostic change in antibody titres in paired serum samples. Rapid diagnosis is possible by detection of *Y. pestis* F1 antigen by immunofluorescence. Small quantities of *Y. pestis'* DNA can be detected in PCR assays. Tissue culture can be performed on various samples e.g. lymph nodes, liver, spleen, lung or bone marrow. Acute-phase serum can be investigated by ELISA or direct immunofluorescence tests for the presence of antibodies against the specific *Y. pestis* F1-capsular antigen. New optical fibre biosensor techniques for plague antigen and antibody detection are under development and have encouraging sensitivity and specificity characteristics but are not yet routinely available. With the support of WHO, a rapid dipstick test for plague was validated in the field and is regularly used in Africa and South America in endemic settings [7].

Transmission of plague through transfusion and transplantation is theoretically possible, however the absence of reported cases and the virulence of the pathogen make asymptomatic bacteraemia unlikely.

Plague can be prevented by reducing contact with wild rodents and their fleas, either through personal protection or by environmental sanitation including rodent and flea control. In natural foci, monitoring programmes should be set so that control can be promptly initiated. Standard precautions and droplet precautions should be applied in healthcare settings during the care of suspected and confirmed plague patients. Plague can be treated with antibiotics. There is no approved vaccine but antibiotics can be used as prophylaxis.

A comprehensive overview for clinicians of antibiotic treatment and post-exposure prophylaxis (PEP) for plague is available through the Centers for Disease Control and Prevention (CDC) resources for clinicians page [8]. After an exposure, the prophylaxis by antibiotics should start immediately. This prophylaxis should be converted into a curative treatment with adequate antibiotics immediately after laboratory specimen-confirmed *Y. pestis*. Control measures during outbreaks include isolation procedures for suspected and confirmed cases, targeted chemoprophylaxis, sanitation and vector and rodent control [9].

Yersinia pestis belongs to the group of bacteria with low resistance to environmental factors. Sunlight, high temperatures and desiccation have a destructive effect and ordinary disinfectants such as Lysol and preparations containing chlorine kill the bacteria within 1 to 10 minutes [10]. *Yersinia pestis* survival viability on manufactured surfaces (stainless steel, polyethylene and glass) remains below four days in laboratory conditions [11]. The hypotheses that soil is a reservoir of *Y. pestis* has been debated, as telluric survival in laboratory and natural conditions has been observed [12]. The epidemical relevance of a telluric reservoir for *Y. pestis* remains unclear [4,6].

Plague in Madagascar

Madagascar is endemic for plague and has been for the past decade the most affected country in the world with around 400 cases of mostly bubonic plague reported annually [13]. The epidemiology of plague in Madagascar shows all-year round transmission in endemic rural foci with zoonotic transmission leading to regular reports of bubonic plague cases [13,14].

Plague was introduced into Madagascar in 1898 from India by rat-infested steamships [15]. The incidence dropped dramatically after the 1930s, but human plague cases did not disappear. The incidence of plague then increased again from 1990 with more than 200 confirmed or presumptive cases reported each year [16]. Recurrent outbreak of bubonic plague were reported in urban settings, notably in Mahajanga city between 1995 and 1998 [17]. In the recent years, several sporadic and clusters of pneumonic plague cases were reported in rural areas and in mid-size cities such as Moramanga (population around 30 000 inhabitants) [13,14,18]. Unsafe burial practices of unrecognised plague cases can lead to significant transmission events, including pneumonic plague cases [18,19].

With the exception of the west coast port of Mahajanga, plague is mainly endemic in highland areas situated above 800 metres in altitude. In these highlands, the human plague transmission season is September to April, while in the Mahajanga area it is July to November [13,15]. *Xenopsylla cheopis* fleas have been known as the primary plague vector in urban areas, whereas *Synopsyllus fonquerniei* fleas have been usually involved in plague transmission in rural areas.

Despite surveillance and control measures to prevent the spread of cases, the elimination of plague has been difficult as the host and reservoir of the bacillus, *Rattus rattus*, is both a domestic and a sylvatic rat. *R. rattus*, is a documented source of *Y. pestis* infections in Madagascar, and progressively acquired resistance to the infection [14,20].

Resistance of *Y. pestis* to antibiotics seems very limited. However, circulating strains are monitored to provide accurate public health information on *Y. pestis* antimicrobial susceptibility. The isolation of the first multidrug-resistant strain of *Y. pestis* in 1995 and the increasing resistance of fleas to insecticides have caused concern [21,22]. The national plague control programme, implemented in Madagascar for several decades, has been hampered by operational and managerial difficulties.

Event background information

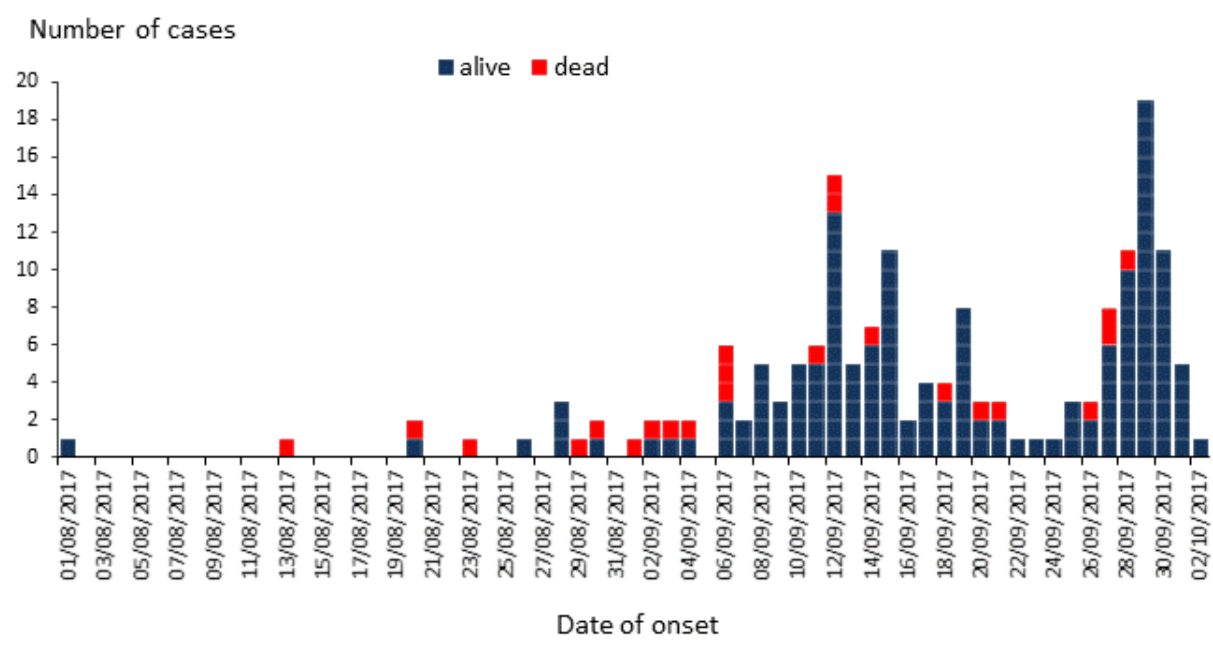
On 23 August 2017, a 31-year-old male from Toamasina developed malaria-like symptoms while visiting the Ankazobe district in the central highlands of Madagascar, [23,24]. On 27 August, respiratory symptoms appeared while he travelled in a shared public taxi from Ankazobe district, a known plague endemic area, to Toamasina via Antananarivo. His condition worsened and he died on 27 August 2017. His body was prepared for a funeral at the nearest hospital in the Moramanga district hospital located between Antananarivo and Toamasina. He was buried in a village close to Toamasina without safety procedures. Subsequently, 31 people who had been in contact with this case fell ill and four of them died [25].

The outbreak was detected on 11 September following the death of a 47-year-old woman from Antananarivo who was admitted to a hospital with respiratory failure caused by pneumonic plague [25]. The public health authorities immediately launched comprehensive field investigations.

On 29 September 2017, the Malagasy health authorities confirmed a fatal case of pneumonic plague in a basketball coach from the Seychelles. The case-patient died in a hospital in Madagascar on Wednesday 27 September while in the country for the Indian Ocean Club basketball championship (23 September to 1 October- Madagascar) [26]. The source of transmission for this case remains unknown. The Madagascar Ministry of Health and the Ministry of Foreign Affairs have informed the Government of Seychelles and authorities of other countries participating in the championship including Comoros, Maurice and Seychelles. Remaining sporting events in the championship took place as closed-door matches in accordance with Madagascar Ministry of Health recommendation [27]. Tracing and investigation of national or international contacts of the case in the preceding days are ongoing. Exposed contacts are prescribed chemoprophylaxis as a precautionary measure and a follow-up is implemented for those considered at havinghigher-risk exposures.

Between 1 August and 3 October 2017, 194 suspected, probable and confirmed cases including 30 deaths (case fatality rate 15.5%) were reported from 20 central, eastern and northern districts in Madagascar. Among these cases there are 124 (64%) pneumonic plague cases including 21 deaths, 68 (35%) bubonic plague cases including seven deaths, and one septicemic plague case and one undetermined plague case [24]. According to WHO, the 124 pneumonic cases reported between 23 August and 3 October 2017 were geographically spread across 12 districts. The capital Antananarivo is the most affected area with 58 cases and nine deaths. The other main affected places are the port city of Toamasina and the rural district of Faratsiho [24].

Figure 1. Distribution of plague cases and deaths by date of onset, 1 August–3 October 2017, Madagascar (n=172 cases where the date of onset is known)



Source: WHO AFRO [23]

Local authorities and international partners are concerned that the outbreak may further spread as it is already present in several cities and the plague epidemic season has already started and usually runs from September to April [26].

Several public health actions have been implemented after the outbreak was notified to WHO on 13 September 2017 [23,24]:

- The Ministry of Public Health is working with WHO to coordinate response to the outbreak, in collaboration with other stakeholders and the communities.
- Active case finding, field investigations of new cases and contact tracing are ongoing in affected areas. In addition, monitoring of contacts of cases as well as provision of chemoprophylaxis is implemented.
- Disinsection of affected areas, including rodent and vector control. Houses of identified cases and close contacts in Antananarivo have been sprayed with insecticides.
- Raising awareness among healthcare workers and providing information to improve case detection and infection control measures. Recommendations for standard management, isolation and treatment of all pneumonic cases and implementation of safe burial practices of dead bodies from suspected, probable and confirmed plague cases.
- Enhancing epidemiological surveillance in the affected and surrounding districts.
- Procuring rapid diagnostic tests (RDTs) to strengthen diagnostic capacity.
- Releasing WHO emergency funds for medical supplies and operational measures. WHO has deployed an emergency response team to provide technical guidance, conduct assessments, support disease surveillance, and engage with communities. Further deployments of WHO staff and response partners through the Global Outbreak Alert and Response Network (GOARN) are underway, as well as increased supplies of antibiotics, personal protective equipment and other supplies.
- Disseminating information on pneumonic plague to health professionals to improve case detection and case management.
- Conducting awareness-raising campaigns through various channels to sensitise people about the disease spread and prevention measures.
- Travel advice for international travellers issued by WHO on 3 October 2017 [28].

ECDC threat assessment for the EU

The likelihood of spread and the public health impact of the plague outbreak in Madagascar

Madagascar is experiencing an outbreak of plague that has involved 194 cases to date, including 124 pneumonic forms. While the number of cases in this outbreak is consistent with what has been observed in previous years, the unusually high proportion of pneumonic forms (64%) is of concern [13,14]. Pneumonic plague is prone to spread in densely populated urban areas in the case of very close contact with a symptomatic case. Controlling the outbreak will depend on the ability of Madagascar to ensure rapid early detection and isolation of cases, their treatment using appropriate infection control measures, comprehensive contact tracing for post-exposure prophylaxis (PEP) and infection prevention and control measures. In contrast, the provision of care by traditional healers, the unsafe burial practices, and the limited application of infection control in healthcare settings may amplify the transmission as previously observed in Madagascar [14,23,24]. The outbreak currently involves several uncontrolled chains of transmission of pneumonic plague and the situation remains unclear at this stage. The infection and death of a foreign visitor to the country without a known source of transmission is of concern.

The likelihood of further spread of the outbreak in Madagascar is considered high until the prevention and control activities implemented by the national authorities with the support of the WHO and international partners allow the outbreak to be controlled in the affected districts [23,24]. According to WHO and as of 2 October 2017, the overall risk at the national level is high [24].

The likelihood of spread to neighbouring countries, including the EU Outermost Regions

The short incubation period of pneumonic plague and the fact that Madagascar is an island limits the risk of spread in the region to incubating visitors travelling by air. Antananarivo is connected to neighbouring islands in the Indian Ocean, including Mayotte and La Réunion (EU OMRs), as well as the capital cities of eastern and southern African countries. No importation of infectious cases of plague to La Réunion and Mayotte has occurred in the past ten years. The fact that a foreign visitor developed pneumonic plague in Madagascar before returning to his home country underlines the fact that an incubating traveller may develop symptoms during a flight and upon return in his/her home country. There is no indication that contacts of the foreign pneumonic case have developed symptoms and they are likely to have received prophylactic antibiotic treatment decreasing the risk of further spread and exportation.

The likelihood of spread of plague at the regional level will depend on the intensity of transmission, mainly in the capital city. The regional risk is assessed by WHO as moderate due to frequent flights to neighbouring Indian Ocean islands [24].

The risk for EU citizens residing in or travelling to the affected areas in Madagascar

According to the Madagascar tourist office, 293 000 tourists visited Madagascar in 2016. The most popular months were October, November and December with around 40 000 visitors each month [30]. In 2016, around 137 000 travellers from 23 EU countries travelled to Madagascar by air, of which 75% originated from continental France. The peak travel months were July, August and October. In addition, there are daily flights to La Réunion and Mayotte, the EU OMRs in the Indian Ocean. Madagascar is also a popular destination for cruises.

The probability of contracting plague in the affected areas in Madagascar is considered to be very low for EU travellers and would most likely result from a direct close contact with a case of pneumonic plague. The probability of importation to the EU through an incubating traveller arriving from Madagascar is considered very low. This probability would be slightly higher among people in the EU or OMRs returning home in Madagascar to visit friends and relatives (VFRs). The Malagasy community in France is estimated at between 100 000 to 140 000 residents mainly in the Ile-de-France region around Paris [https://mg.ambafrance.org/Une-premiere-etude-sur-la-diaspora-malgache-de-France].

The risk of international spread of plague appears very low according to WHO travel advice based on the available information as of 2 October 2017[24]. ECDC is closely following the situation, and the level of risk will be reassessed in light of further available information about the outbreak and the occurrence of multiple foci of transmission within the capital city, Antananarivo.

Disclaimer

ECDC issued this risk assessment document on the basis of an internal decision in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control. In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter with their respective advantages and disadvantages. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written under the coordination of an Internal Response Team (IRT) at the European Centre for Disease Prevention and Control (ECDC). All data published in this risk assessment are correct to the best of our knowledge on 5 October 2017. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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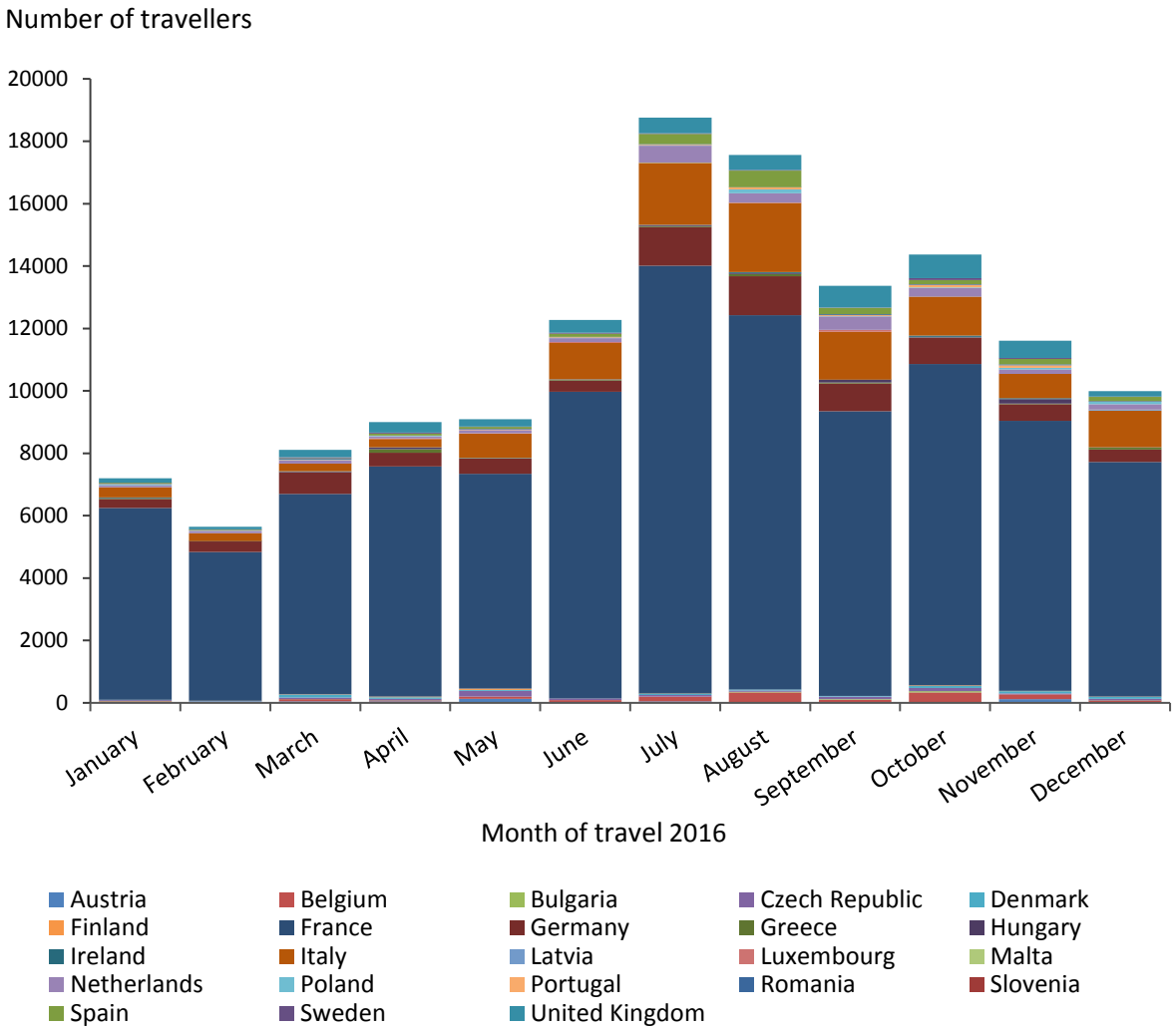
Annex. Estimated number of travellers from the EU to Madagascar by month in 2016

Figure 1. Estimated number of travellers from the EU to Madagascar by month, 2016, EU/EEA



Source: IATA