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MISSION REPORT

Assessing the yellow fever outbreak in Angola

European Medical Corps mission undertaken in the framework of the European Union Civil Protection Mechanism

10 – 20 May 2016

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This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Josep Jansa and Ettore Severi.

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Abbreviations

Bti	*Bacillus thuringiensis israelensis*
CFR	Case–fatality ratio
EMC	European Medical Corps
GOARN	Global Outbreak Alert and Response Network
ICG	International Coordinating Group on vaccine provision
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHR	WHO International Health Regulations
INSP	Instituto Nacional de Saúde Publica, Luanda
MoH	Ministry of Health
PCR	Polymerase chain reaction
ELISA	Enzyme linked immunosorbent assay

Overview of the mission*

The mission was initiated by the European Commission (EC) and the European Centre for Disease Prevention and Control (ECDC), in agreement with the Government of the Republic of Angola. The deployment of the expert team took place in the framework of the European Union Civil Protection Mechanism and employed the recently established European Medical Corps. The Emergency Response Coordination Centre (ERCC) of the Directorate-General Humanitarian Aid and Civil Protection (DG ECHO) organised deployment of the team and ensured coordination with other EU services. ECDC deployed two experts and provided back-office epidemiological support during the mission and the report preparation. DG Health and Food Safety (DG SANTE) oversaw the mission from a policy perspective. The EU Delegation in Angola provided important logistical support, background and contact information.

The team consisted of Josep Jansa, team leader (ECDC); Maria Isabel Aldir, clinical expert (Hospital Egas Moniz–Centro Hospitalar de Lisboa Ocidental, Portugal); Jonathan Baum, technical support (Mercator Fellowship, Germany); Laurent Defrance, ERCC liaison officer (DG ECHO, European Commission); Joana Haussig, epidemiologist (Robert Koch Institute, Postgraduate Training for Applied Epidemiology, Germany); Amparo Laiseca, regional health expert (DG ECHO, European Commission); Ettore Severi, epidemiologist (ECDC); and Veerle Vanlerberghe, yellow fever expert (Antwerp Institute of Tropical Medicine, Belgium).

Summary

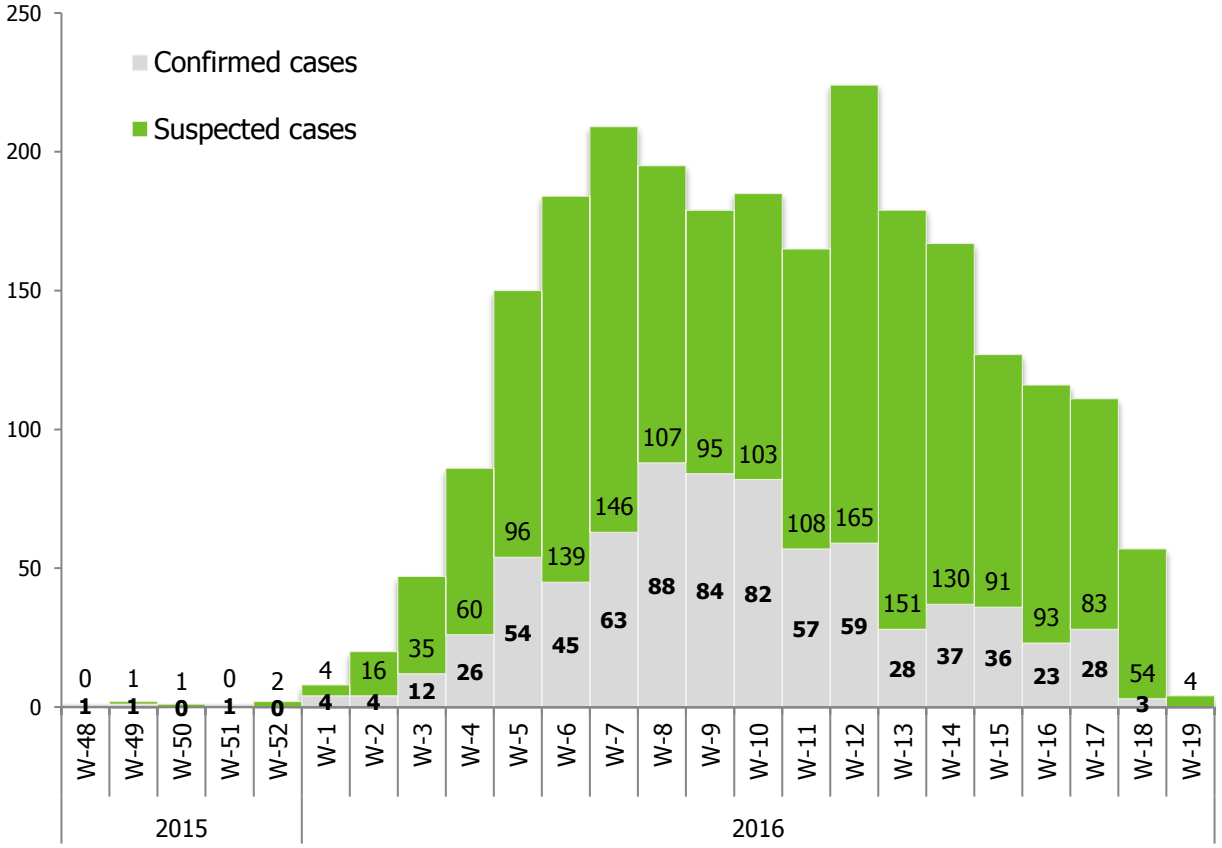
An epidemic of yellow fever is currently affecting the Republic of Angola. The first yellow fever cases, reported in the province of Luanda, had onset of symptoms in December 2015. Since then, all provinces have reported cases. Cases have also been imported into other countries in the region, raising concern about the international spread of the epidemic. In this context, the European Commission, in close cooperation with ECDC, deployed a team of public health and humanitarian experts in Angola. The mission team reviewed the epidemiological situation of yellow fever in Angola, assessed the implemented control measures (to later advise the Angolan health authorities), evaluated the risk of importation of yellow fever to the EU, assessed the risk for EU citizens, and provided advice to the European Commission. The mission was organised in agreement with the Government of Angola and in close coordination with the World Health Organization (WHO). The mission was conducted in the framework of the European Union Civil Protection Mechanism and, for the first time, employed the newly established European Medical Corps.

Since the beginning of the epidemic and as of 25 May 2016, 736 yellow fever cases were laboratory confirmed. Eighty-eight of these confirmed cases were fatal (CFR of 12%). The first suspected case presented with yellow fever symptoms to a private clinic on 5 December 2015 (Figure 1). The patient – from Viana, Luanda province, a densely populated outskirt municipality of Luanda – was confirmed on 21 January 2016. Since then, cases have been reported in all 18 provinces of Angola; confirmed cases were reported in 14 provinces.

As of 15 May 2016, the Angolan Ministry of Health (MoH) has notified 2 420 suspected yellow fever cases, 298 of which were fatal (CFR of 12%). The epidemic curve (Figures 1 and 2) shows that the highest number of suspected and confirmed cases was reported in February and March 2016, with a peak of notification at the end of February, when more than 80 confirmed cases per week were reported. Since April, the number of new cases has declined in Angola. In the two most affected provinces of Luanda and Huambo, it has decreased to an average of 30 cases per week. However, transmission of yellow fever has spread to new areas and increased in Benguela province. Overall, 70% of cases are in males, with a large proportion of men between 15 and 30 years of age.

* The views expressed in this document may not in any circumstances be regarded as stating an official position of the European Commission.

Figure 1. Distribution of suspected cases of yellow fever by week of onset and confirmation status, Angola, 21 January–15 May 2016 (n=2 420), as of 25 May 2016



The epidemic curve should be interpreted with caution because a significant proportion of cases was probably never diagnosed or reported, particularly at the early stages of the epidemic. Furthermore, the epidemic curve presents cases by week of onset, which implies that the number of cases recorded during the most recent weeks will be an underestimate of the actual case numbers because of the time between onset of symptoms, diagnosis and reporting. Numbers after week 17 are therefore considered incomplete.

The recent decrease in the number of reported cases, mainly in Luanda and Huambo, the two largest urban areas of the country, is largely due to the implementation of vaccination campaigns. At the time of writing, Benguela, the third most populated urban area in Angola, is reporting an increasing number of cases, while some areas report yellow fever transmission for the first time and other areas continue to report yellow fever transmission. This clearly indicates that the epidemic is not yet under control.

The first mass vaccination campaign started on 2 February 2016. As of 15 May 2016, the International Coordination Group for yellow fever vaccine had released 11.7 million doses for Angola. Vaccination campaigns were conducted in the province of Luanda (February and March) and in selected municipalities in Huambo and Benguela provinces (April). Campaigns are currently conducted in selected municipalities in the provinces of Benguela, Cuanza Sul, Huambo, Huíla, and Uige. Due to limited vaccine supplies, the current yellow fever vaccination strategy focuses on mass vaccination campaigns for all people aged six months or older in municipalities where local yellow fever transmission has been confirmed (priority areas). As the strategy does not allow intervention in areas not yet affected, vaccinations cannot be administered in order to prevent the establishment of transmission. Vaccine coverage analysis has shown that adult males are less likely to get vaccinated than women and children, which could explain why young males are overrepresented among the most recent cases.

The effectiveness of the vector control activities is jeopardised by the limited availability of data on vector presence, data on infestation levels, insufficient resources, and irregular availability of insecticides. The conditions favouring vector abundance are likely to change in the southern and central provinces when the rainy season ends in April/May. Transmission rates will decrease because vector control measures and vaccination efforts will be positively influenced by the drier weather. In the northern provinces, the environmental conditions for mosquito transmission will remain suitable, and new cases will to continue to occur until the vaccination of the targeted population has been completed.

Currently, all regions in Angola should be considered as areas at high risk of transmission of yellow fever. Large urban areas and the Angolan northern provinces of Zaire, Uige, Malange and Lunda Norte represent a significant risk for international spread. This is particularly true for the province of Cabinda, where a confirmed case of yellow fever reported by the Democratic Republic of Congo was infected. Imported confirmed cases from Angola were reported in the Democratic Republic of the Congo (41 cases), Kenya (2 cases) and China (11 cases).

Viraemic patients travelling to areas where suitable vectors and susceptible human populations are present risk causing local transmission. Such areas exist in most of the intertropical zones of Africa, the Americas and Asia.

Strengthening control measures to control of the epidemic in Angola and thus prevent an international spread is essential. This includes preventing viraemic travellers from acting as a source of transmission in receptive areas abroad.

The team deployed to Angola identified the following actions that could contribute to strengthening the efficiency of control measures in Angola:

- The provision of standardised protocols for the clinical management of suspected yellow fever cases at the provincial and national levels and the development of standardised algorithms for case ascertainment at the emergency department level.
- The consistent application of case definitions at all levels, combined with improved reporting of suspected cases, particularly in areas such as Cabinda province, from where several cases were exported. All cases meeting the case definition, including those reporting a history of vaccination and those testing positive for malaria infection, should be reported, regardless of severity.
- Laboratory capacities for differential diagnosis of flavivirus IgM-positive samples should be strengthened.
- Accelerating vaccination campaigns in areas at increased risk for the spread of the disease:
  - Densely populated urban areas
  - Municipalities with a highly mobile population such as Lubango (Huíla)
  - Areas along international borders with presence of *Aedes* mosquitoes and suitable for vector transmission – even during the dry season – such as Cabinda province
  - Municipalities surrounding areas of local transmission should be prioritised in order to create a vaccinated buffer zone and prevent the further spread of yellow fever.
- Implementation of mop-up campaigns in local transmission areas with low vaccination coverage and new cases. This can prevent transmission in areas that had already been targeted by vaccination campaigns, e.g. in Luanda province. Understanding the reasons for not getting vaccinated can help public health authorities to implement interventions to increase vaccine acceptance. Additional vaccine supplies should be made available by the international community to allow vaccination campaigns in additional municipalities where local transmission is not yet confirmed. The international community and local authorities should also ensure that a sufficient stock of yellow fever vaccine for routine childhood vaccinations remains available.
- Vector control activities in areas with local transmission should be performed as soon as a suspected case is detected.

The deployment of international human resources through GOARN or international NGOs would be helpful to reach higher vaccination coverage rates in a shorter time and to strengthen surveillance activities.

Representatives of EU embassies in Angola reported that most EU residents in Angola were vaccinated for yellow fever. People who cannot be vaccinated have been a matter of concern, e.g. newborn babies and people with underlying health conditions. For these groups, personal vector control measures should be taken.

The risk of importation of the virus to the local competent vector population in the EU through viraemic travellers from Angola is considered to be moderate, particularly in areas where *Aedes aegypti* is present (Madeira). Potential local transmission of yellow fever in regions of the EU/EEA where *Aedes albopictus* is present cannot be ruled out if the virus is introduced by a viraemic traveller. Some EU Overseas Countries and Territories and Outermost Regions are located in the intertropical area with large populations of competent *Aedes aegypti* mosquitoes. In these areas, the likelihood of importation is low because of the limited travel patterns with Angola, but the risk of local transmission would be increased, should introduction occur, because of vector abundance.

In addition to enforcing yellow fever vaccination for all travellers to epidemic areas, the team identified the following options to consider:

- Preventing viraemic travellers from entering the EU by enforcing the WHO IHR (International Health Regulations) emergency committee recommendation that only travellers with proof of a valid vaccination record for yellow fever are allowed to leave Angola [1]. While this recommendation is supposedly enforced, neither the mission team members nor their fellow travellers were asked by airport authorities to present their vaccination documents when exiting the country. Vaccination records should also be checked at land border crossings and international seaports.

- Alternatively, EU Member States, particularly those with established populations of suitable *Aedes* mosquitoes, could prevent the arrival of viraemic travellers by requesting proof of valid vaccination when issuing a visa.
- Studies assessing the competence of the European *Aedes albopictus* mosquito populations and their capacity to transmit yellow fever should be reviewed.
- Clinicians should consider yellow fever in sick travellers returning from affected areas.
- Suspected and confirmed patients should be prevented from being bitten by *Aedes* mosquito vectors (for example through mosquito nets or insect repellents) to decrease the risk for human-to-mosquito-to-human transmission.

Country support

Ministry of health

Miguel Dos Santos de Oliveira (Angolan Ministry of Health (MoH), yellow fever technical team at the Angolan Ministry of Health), António Chimbili (Ministry of Health, Huíla).

EU delegation and other stakeholders

Carmen Lloveres (EU Delegation, Angola), Fernando Trabada (EU Delegation, Angola), Carlos Navarro-Colorado (WHO incident manager), Hernando Agudero (WHO representative), Dinorah Calles (US CDC), Tatiana Lanzieri (US CDC), Ousmane Faye (Pasteur Institute, Dakar), Paolo Baladelli (United Nations, resident coordinator in Angola), Helena Valencia (MSF, Barcelona).

Background and justification

Since December 2015, the Republic of Angola has been experiencing an outbreak of yellow fever in the central province of Luanda. Currently, all 18 provinces of the country have reported suspected cases; 14 provinces also reported confirmed cases. On 24 April 2016 (when the mission was approved), the Angolan MoH reported 2 023 cases and 258 deaths [2]. Yellow fever cases linked to transmission in Angola were also reported from China, Kenya, and the Democratic Republic of the Congo.

In response to the outbreak, a large-scale vaccination campaign was launched, initially aiming to vaccinate 6.7 million people [3]. However, vaccination efforts were hampered by the lack of vaccine at the international level (despite the availability of funds in the country) and by logistical issues in Angola (e.g. inadequate number of teams for vaccination campaigns) [4].

According to WHO estimates, 34 countries in Africa have conditions suitable for local (autochthonous) yellow fever transmission, comprising a total population of 508 million people. The 24 March risk assessment published by ECDC considered the risk of importation of the virus into the European competent vector population by viraemic travellers to be limited. However, the competent vector *Aedes aegypti* is present in some areas of Europe and the European Union (e.g. the island of Madeira). Angola also has a considerable European population.

In view of the situation, the European Commission and ECDC saw added value in sending a team of public health and humanitarian experts to Angola, with the aim of understanding the underlying causes of the outbreak, identifying the public health risks for the EU, assessing the humanitarian situation, evaluating response measures applied by the Angolan authorities and other organisations, and advising the Angola authorities on appropriate response measures.

The mission was organised in agreement with the Government of Angola and coordinated with WHO. The mission was prepared and carried out within the framework of the European Union Civil Protection Mechanism and employed the recently established European Medical Corps.

Objectives

- To assess the outbreak of yellow fever in Angola, determining its epidemiological characteristics, including the identification of at-risk groups, distribution and severity of cases, the dynamics of the outbreak, areas with local transmission, vaccine coverage, and virus circulation
- To assess the risks for the population of Angola with regard to the dynamic of the epidemic and the ongoing measures for response
- To assess and estimate the geographical spread and duration of the epidemic and the risk of further regional spread

- To evaluate the risk to European citizens residing in or visiting Angola
- To evaluate the risk of importation into areas of the EU where competent vectors are present, with a view to advise on appropriate public health measures in the EU/EEA
- To review the response measures taken by the local authorities, bilateral/multilateral partners, and non-governmental organisations.

Methodology

Objectives were addressed through the following activities:

- Meetings with senior public health officials from the MoH and the national public health directorate of Angola
- Meetings with the WHO incident manager, the WHO country representative and other WHO officials
- Meetings with national and international actors involved in the field: medical staff, entomologists and vector control technicians from the Cuban Cooperation team, epidemiologists from the US Centers for Disease Control and Prevention (CDC), experts from CDC China, medical and other staff from Médecins sans Frontières/Doctors without Borders, and United Nations (e.g. UNICEF) staff
- Reviewing available epidemiological information
- Field visits: healthcare facilities (hospitals, primary care centres), provincial and municipal health authorities, public health activities (vaccinations, risk communication, vector control).

Disease background information

Yellow fever is an acute viral haemorrhagic vector-borne disease affecting humans and non-human primates in tropical areas of Africa and South America. It is caused by a virus of the *Flavivirus* genus of the Flaviviridae family and transmitted by infected mosquitoes of *Aedes* and *Haemagogus* genera.

The virus originated in Africa and was introduced to the Americas a few hundred years ago. The disease is transmitted by several *Aedes* mosquito species in sylvatic cycles and by *Aedes aegypti* in urban cycles. Monkeys and humans act as amplifying hosts [5].

There are uncertainties about the capacity of *Aedes albopictus* to transmit yellow fever. The competence of *Aedes albopictus* for the transmission of the yellow fever virus has been demonstrated in Brazil using a Brazilian strain of yellow fever virus. Brazilian *Aedes albopictus* mosquitoes were infected at rates similar to those of Brazilian *Aedes aegypti* and dissemination was observed in the salivary glands. Although these dissemination and infection rates were lower than those observed for *Aedes aegypti*, the ability of *Aedes albopictus* to transmit the yellow fever virus cannot be ruled out in areas where infestation and biting indexes are high [6-8].

Yellow fever is endemic in 34 countries across sub-Saharan Africa and in 13 countries across South America [9]. In 2013, 130 000 (95% CI: 51 000–380 000) severe cases and 78 000 (95% CI: 19 000–180 000) deaths are estimated to have occurred in Africa, accounting for around 90% of all global cases [10]. Local transmission of yellow fever has never been detected in Asia, although the competent vector is present in south and south eastern areas of the continent.

In endemic countries, yellow fever is maintained in a cycle involving mosquitoes and non-human primates. In Africa, there are three cycles of yellow fever transmission: the sylvatic cycle, the intermediate or rural cycle, and the urban cycle. Infected mosquitoes that bite humans who enter the forest give rise to sporadic cases of yellow fever. Infected humans who return to urban areas where the highly effective and anthropophilic *Aedes aegypti* vector is present, may initiate human-to-human transmission cycles. Large epidemics, with tens of thousands of deaths, have been recorded in Africa.

Around 85% (50% to 99%) of infections in humans are either asymptomatic or result in mild illness [11]. After an incubation period of three to six days, infection develops in one or two phases. The initial symptoms include sudden onset of fever, chills, severe headache, back pain, general body aches, nausea, vomiting, fatigue and weakness.

Most people improve after the first phase but around 15% of cases, after a brief remission, develop the severe form of the disease, characterised by high fever and jaundice, and in some cases bleeding, eventually resulting in shock and multiple organ failure. Among those who develop severe disease, up to 50% may die. There is no specific treatment for yellow fever. Infection provides lifelong immunity.

Yellow fever infection is challenging to diagnose, especially during the early stages. Differential diagnoses for yellow fever include malaria, dengue, leptospirosis, viral hepatitis and poisoning. The virus can be detected in blood specimens by reverse transcription polymerase chain reaction (RT-PCR), antigen-capture or viral isolation. For primary arbovirus infections, a serological diagnosis can be made by detection of specific IgM antibodies one week after infection; for secondary arbovirus infections, IgM *and* IgG have to be detected [12].

Two previous outbreaks of yellow fever have been documented in Angola, one in 1971 (65 cases) and one in 1988 (37 cases).

Prevention and outbreak control

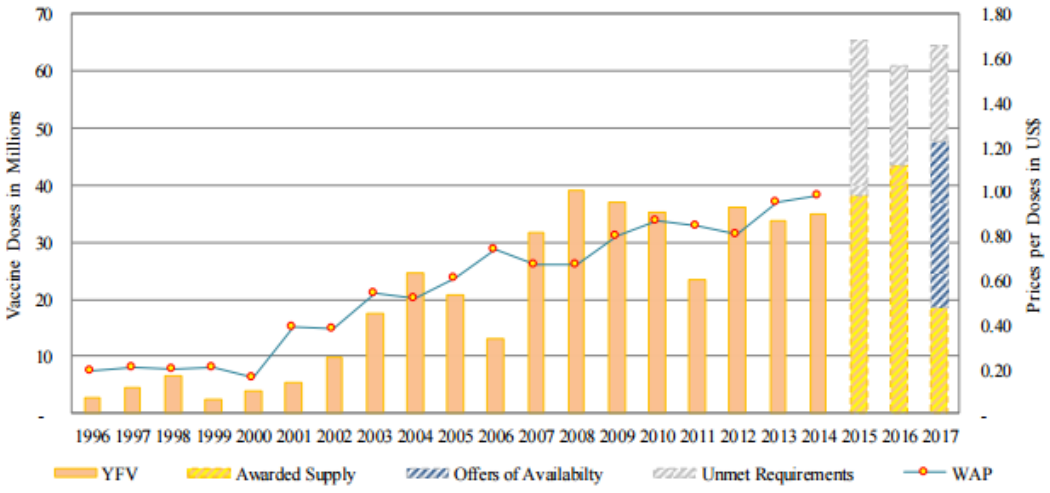
Yellow fever is effectively prevented through vaccination with the live attenuated vaccine that was first developed in 1937. The vaccine is recommended for people aged ≥9 months. Some adverse effects associated with the vaccine have been reported, and a case-by-case assessment of the risks and benefits of yellow fever vaccination should be considered for some risk groups, such as older people or those with underlying health conditions [13].

The vaccine is recommended for individual protection of travellers at risk of exposure to yellow fever and to prevent international spread of the disease from endemic countries to countries with competent vectors. The period of protection provided by yellow fever vaccination, and the term of validity of the certificate, has been changed from 10 years to life for those vaccinated according to a World Health Assembly resolution, which will go into effect in July 2016. On 19 May 2016, the Emergency Committee of the International Health Regulations (2005) advocated the immediate application of the policy of one lifetime dose of yellow fever vaccine in light of the limited worldwide vaccine supply [1].

Mass vaccination campaigns are the most effective public health strategy to control yellow fever outbreaks. The yellow fever vaccine stockpile is managed by the International Coordinating Group (ICG) on vaccine provision for yellow fever control. ICG has representatives from WHO, UNICEF, Médecins sans Frontières (MSF) and the International Federation of Red Cross and Red Crescent Societies (IFRC). The stockpile is managed through a revolving fund held by WHO, by which supplies can be advanced all year round [14].

Shortage of yellow fever vaccine has recently become a concern. According to UNICEF, the forecast for vaccination activities worldwide for 2015–2017 was for 64 million doses per year, but only 35 million doses are produced – 45% below the required quantity. Additional offers made to UNICEF for 2015–2017 will decrease this shortage. UNICEF expects production to increase to reach 47.6 million doses annually by 2017 (Figure 2) [15].

Figure 2. Worldwide yellow fever vaccine supply through UNICEF and demand forecast for 2015–2017



** WAP: weighted average price*
Source: UNICEF Supply Division/GA VI SDF v. 10

Complementary preventive measures include using insect repellent and wearing protective clothing. Mosquito control can contribute to preventing yellow fever, and is of utmost importance in situations where vaccination coverage is low or the vaccine is not immediately available. Mosquito control includes eliminating sites where mosquitoes can breed and killing adult mosquitoes and larvae by using insecticides and larvicides in areas with high mosquito density. Community involvement through activities such as cleaning household drains and covering water containers where mosquitoes can breed is a very important and effective way to control mosquitoes [16] but requires some time for set-up and implementation.

Event background information

On 22 January 2016, the IHR focal point for Angola notified WHO of an ongoing yellow fever outbreak. The first cases reported were in two males from the municipality of Viana, Luanda province. The first patient presented with

yellow fever symptoms to a private clinic on 5 December 2015 [17]. On 19 January, samples from three patients were confirmed for yellow fever infection by PCR at the Zoonosis and Emerging Disease Laboratory of the National Institute for Communicable Diseases in Johannesburg, South Africa. On 29 January, the samples were also confirmed by the regional yellow fever reference laboratory at the Pasteur Institute in Dakar, Senegal.

Following the confirmation of cases of yellow fever infection in Luanda province and other provinces of Angola, the national reporting system was enhanced to rapidly gather epidemiological information on suspected cases and collect samples.

Cases were categorised as 'suspected' when presenting with fever and icterus, with or without haemorrhagic symptoms, and as 'confirmed' when testing positive for yellow fever by IgM serology and/or by PCR.

Suspected cases that were not tested – or tested negative by serology or PCR – are categorised as 'non-confirmed suspected cases'. Suspected cases who reported that they had been previously vaccinated (showing a vaccination record or self-reporting vaccination) are routinely reported as 'vaccine cases' and can therefore not be categorised as a 'non-confirmed suspected case', regardless of subsequent IgM results.

In April and May, the reporting delay for confirmed cases was about two weeks. The data presented are considered incomplete from week 17 onwards.

From 21 January to 15 May 2016, the Angolan MoH notified 2 420 suspected yellow fever cases, 736 of which were confirmed. Among the 2 420 cumulative suspected cases, 298 were reported as deaths (case fatality ratio (CFR): 12%). Among the 736 confirmed cases, 88 died (CFR: 12%).

The onset of the first case was on 5 December 2015. The highest number of suspected and confirmed cases was reported between the first week in February and the first week in April (weeks 5 to 14). At the end of February and the beginning of March (weeks 8 to 10), more than 80 confirmed cases were reported every week. During the month of April, about 30 confirmed cases were reported per week.

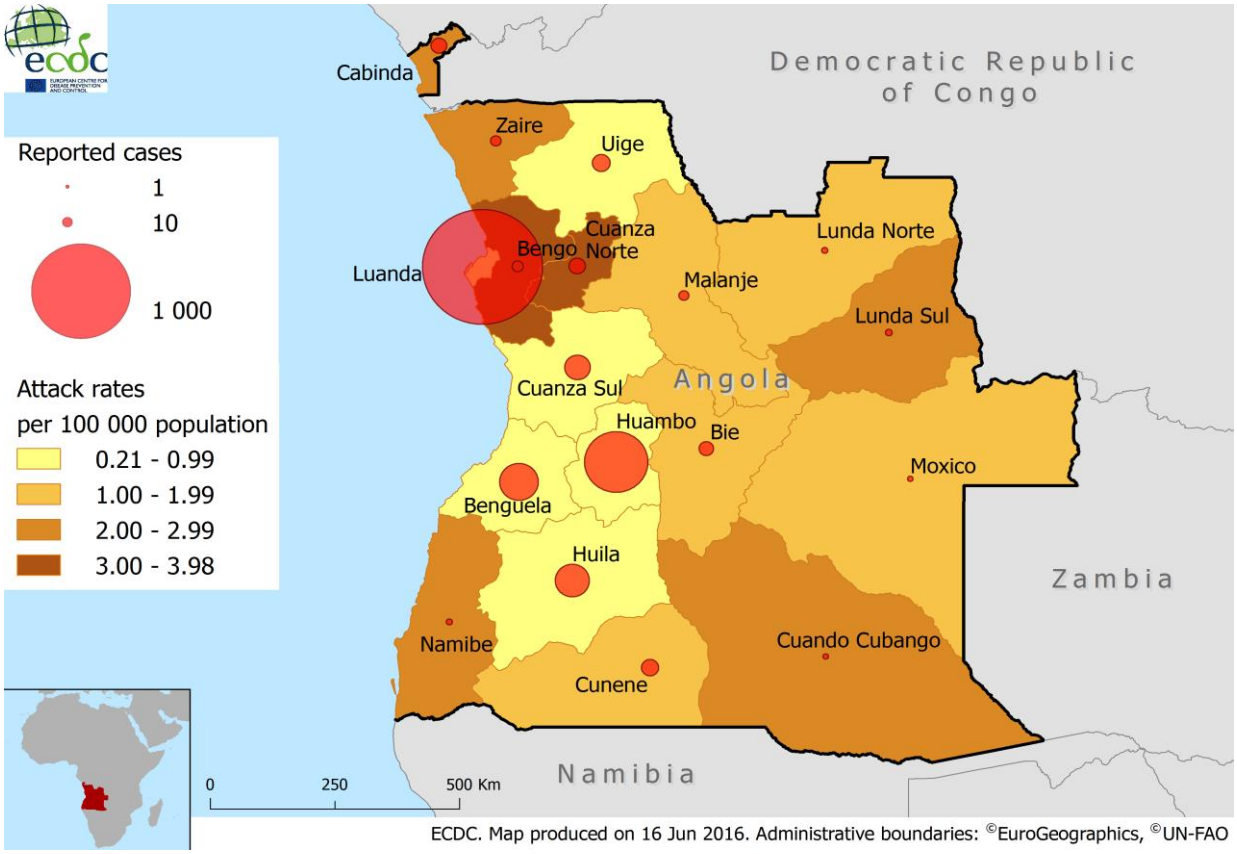
The first confirmed cases were reported in Viana, Luanda province, a densely populated outskirt municipality of Luanda. These cases were linked to the *Quilometro 30* market, the country's largest outdoor market. In the following months, suspected cases were reported in all 18 provinces; confirmed cases were reported in 14 provinces. As of 15 May, Luanda province has reported the highest number of cases. The outbreak peaked between the last week in February and second week in March 2016 (weeks 8 to 10), with ≥50 confirmed cases reported per week. Since then, the number of cases has steadily decreased: five cases each were reported in the fourth and fifth week of April (weeks 16 and 17). In addition to Luanda province, the five provinces of Benguela, Cuanza Sul, Huambo, Huíla and Uige have experienced local transmission.

The province of Huambo, central Angola, reported the second highest number of confirmed cases after Luanda province. The peak of reported cases was observed from the fourth week in February to the third week in March (weeks 8 to 11), with ≥10 confirmed cases reported per week, peaking at 20 confirmed cases in week 9. Over the last few weeks the number of confirmed cases consistently decreased: in week 17, four confirmed cases were reported.

A different trend was seen in Benguela province, the third most affected province after Luanda and Huambo, where the number of reported confirmed cases per week increased during April 2016, with the outbreak peaking in week 17 (16 confirmed cases).

Most confirmed cases were in people between 15 and 30 years of age, and 70% of confirmed cases were males. The gender imbalance is identifiable in all age groups except in children <10 years of age.

Figure 3. Distribution of suspected/confirmed yellow fever cases and areas of local transmission, Angola, as of 10 June 2016 (3137 suspected cases and 847 confirmed cases)



Preparedness

Emergency preparedness was good in the visited hospitals where beds were reserved for yellow fever cases. A protocol for case management was available, even though it has not been harmonised at the national level. Beds are fitted with mosquito nets or in rooms with controlled temperature, but the nets are not always properly tucked under.

Yellow fever surveillance

The guidelines of the Angolan MoH specify the following procedure for the notification of suspected cases to the national yellow fever surveillance system:

A patient who meets the case definition is referred to a higher-level health facility, e.g. a provincial hospital. A standardised epidemiological reporting form is completed. Deaths and suspected cases should be notified immediately to the national surveillance system. For severe cases, a sample is taken for laboratory testing. Samples are sent daily to the central laboratory. Laboratory results are sent via email to the provincial health directorate and communicated via telephone to the treating clinicians. Within 48 hours of notification, a surveillance team should be dispatched to investigate the case. Surveillance teams comprise epidemiologists, clinicians and laboratory technicians. The teams perform active case and contact finding at the community level in a radius of 200 metres around suspected cases.

It is not always clear whether the registration and notification of cases is conducted at the first health facility visited by the patient or at the referral institution. At the beginning of the epidemic, sample collection procedures were not clear.

Laboratory diagnostics

Polymerase chain reaction (PCR) and Enzyme linked immunosorbent assay (ELISA) are used for the laboratory confirmation of yellow fever. While PCR detects the RNA of the yellow fever virus, ELISA detects virus-specific antibodies (IgG/IgM). The criteria for confirmation of a yellow fever case are detection of viral RNA, yellow fever-

specific IgM, or a fourfold or greater rise in specific serum IgG levels* (especially for flavivirus secondary cases). A recent yellow fever vaccination and IgM/IgG positivity due to other flaviviruses (cross-reaction) have to be ruled out for interpreting serology results.

For yellow fever, the IgM detection in secondary infections can be as short as three days after onset of symptoms [1]. This is especially important in Angola, where circulation of the dengue virus has been reported over the past three years. According to the MoH, dengue outbreaks have not overlapped with yellow fever outbreaks. IgM can also persist for a long period after vaccination (up to four years [2]). Positive results should be confirmed with a plaque-reduction neutralisation test to differentiate between flaviviridae and the wild and vaccine type of yellow fever virus.

During the first three to four days of illness and up to 10 days after onset of symptoms, yellow fever genetic material can be detected in the serum by virus isolation or nucleic acid amplification testing (RT-PCR). However, a negative result cannot rule out the possibility of yellow fever because by the time overt symptoms are recognised, the virus or viral RNA can be already undetectable.

Initially, confirmation of cases was performed at the Institut Pasteur in Dakar, Senegal. Since 6 March, the Instituto Nacional de Saúde Publica (INSP) in Luanda performs all yellow fever IgM ELISA and RT-PCR tests. The time necessary to perform the test is approximately two hours. All samples of suspected cases in Angola are sent to Luanda where diagnosis is centralised in the INSP. If samples are positive for yellow fever IgM, rapid diagnostic tests (RDT) for dengue (NS1, IgM, IgG) and Zika are performed. All positive test results for yellow fever (PCR and/or IgM) are currently discussed during a case confirmation meeting† held in Luanda twice a week. In the meeting, suspected cases are categorised as 'confirmed' or 'not confirmed' (vaccine related, negative test results, or no samples available for confirmation) based on information contained in the epidemiological reporting form and the patient's vaccination history. If necessary, a sample is sent to the regional reference laboratory in Dakar. All suspected samples are also tested for malaria by rapid diagnostic testing and for chikungunya (RDT IgM/IgG).

During the initial phase of the epidemic, the number of requests for testing exceeded capacity. Currently, laboratory capacity is sufficient to test an average of about 40 samples per day. The average turnaround from taking samples to informing the treating clinician is about one to two weeks.

Technicians at the Institut Pasteur in Dakar support the INSP in diagnostic testing and quality control procedures.

Malaria transmission is endemic in Angola, particularly during the rainy season from November to May. Malaria transmission appears to have been particularly strong in the early months of 2016. Of 232 yellow fever-positive samples tested for malaria, 110 (47.4%) were positive for malaria as well. Co-infection of yellow fever with dengue and chikungunya has been identified as well, however with the available diagnostics techniques it was not possible to discern whether dengue and chikungunya were past or acute infections.

Case management

By law, the health system in Angola is universal and free. However, services are often drastically limited due to the limited availability of medications and human resources. The health system provides services at different levels, from health posts offering basic services to more advanced health centres and hospitals at the municipal, provincial and tertiary levels.

In addition to the public system, the private health sectors offers services to those who can afford it. Private clinics are not always integrated in the country surveillance system. A considerable proportion of the population in Angola (no numbers available) still relies on traditional medicine for their primary healthcare needs. This explains why many patients present late at the hospital or health centre.

During the initial phase of the yellow fever epidemic, all patients in Luanda Province were sent to the two main central hospitals *Josina Machel–Maria Pia* and *Américo Boavida* or the provincial hospital *Geral de Luanda*, where dedicated wards for yellow fever patients were available. As the number of cases grew, yellow fever wards were also established in municipal hospitals. According to the MoH, all hospital rooms have to be equipped with mosquito nets or devices to control the room temperature.

The production of guidelines for the establishment of treatment wards and of guidelines on clinical treatment was left at the discretion of the institutions, as was the production of algorithms/flowcharts for the identification and triage of suspected cases in emergency departments.

The medical care provided to yellow fever patients was appropriate given the available resources. However, treatment varied from hospital to hospital. The differential diagnosis differed and depended on the availability of

* Especially for flavivirus secondary cases

† The case confirmation team consists of staff from INSP, the MoH surveillance department, WHO, the Cuban Cooperation team, and the US CDC.

rapid diagnostic tests. Moreover, tests were often duplicated at the reference laboratory in Luanda, resulting in a waste of resources.

The complexity of the situation is also a result of the fact that all flaviviruses can give similar clinical pictures, namely acute febrile syndromes, sometimes with haemorrhagic manifestations. In addition, the identification of suspected cases is further complicated by the ongoing malaria epidemic. Since the clinical presentation of both diseases can be similar at the early stages, yellow fever misclassification is possible.

Immunisation strategy

The first yellow fever mass vaccination campaigns in Angola started on 2 February 2016. As of 15 May, ICG released 11.7 million doses of yellow fever vaccine for Angola. Vaccination campaigns have taken place in the province of Luanda and are currently in progress in selected municipalities in the provinces of Benguela, Cuanza Sul, Huambo, Huíla and Uige (Annex: Table 1).

The current yellow fever vaccination strategy focuses on mass vaccination of the population six months of age or older in provinces and municipalities where local yellow fever transmission has been confirmed. The strategy is implemented in accordance with ICG policies due to limited vaccine supplies.

Vaccination sites are often located in health centres, schools and churches. Registration forms record the age and pregnancy status but not gender, HIV status or any other health condition. The actual vaccination takes place at a dedicated vaccination station. Finally, vaccination records are filled out and handed over at a third station.

Vaccines are kept in cold storage boxes with cold accumulators and diluted before use. The cold chain supply is maintained with refrigerators and cooling boxes which are maintained at the municipal and provincial levels. The temperatures of the cold chain supply is checked twice a day.

The mission team was told about cold chain problems, reconstituted vaccines, and syringes already drawn up the day before.

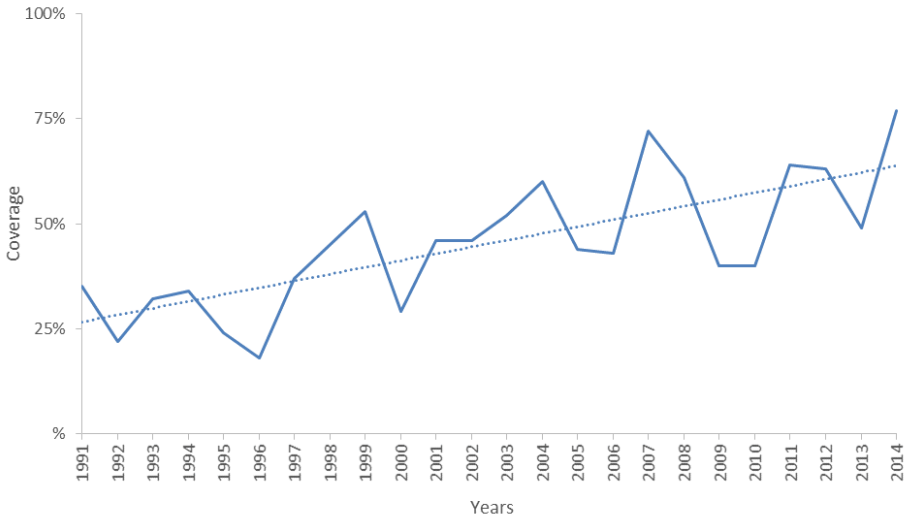
During a vaccination campaign only the expected required amount of doses plus 10% is distributed to the municipalities. Unused doses are returned to the provincial storage facility. At the end of the provincial vaccination campaign, leftover vaccine is returned to the national storage facility.

Although gender was not recorded in the vaccination campaigns, it was observed that adult males were less likely to get the vaccine than women and children. Epidemiological analysis shows that men are at particular risk: the majority of cases were in men between 15 and 30 years of age.

Monitoring of adverse events following immunisation is currently not implemented, but a protocol was under development and was scheduled to go into effect in week 21–2016.

In Angola, yellow fever vaccine was integrated in routine immunisation in 1980 (Figure 4). Currently, vaccine stocks for routine childhood yellow fever vaccinations for children of 9 months are very low.

Figure 4. Yellow fever vaccine coverage of target population, Angola, 1991–2014



Source: WHO/UNICEF estimates. Available from: http://www.who.int/immunization/monitoring_surveillance/data/ago.pdf

Trainees of the Angolan field epidemiology training programme and US CDC staff performed a KAP (knowledge, attitudes and practices) survey on yellow fever vaccination that reached 302 men interviewed in four municipalities

of Luanda. Only 32% of respondents identified mosquitoes as the source of transmission of yellow fever virus. Among unvaccinated men, 42% stated they did not know where to get vaccinated and 21% considered the vaccine as dangerous. Of those that would like to get vaccinated, 25% stated they did not have time or were unable to attend due to work, and 20% stated they did not want to wait in line for the vaccination.

Vector control activities

Vector control in Angola is mainly directed towards controlling the malaria vector *Anopheles*. However, the same methods are also applied to other disease-transmitting mosquitos, such as the yellow-fever-transmitting *Aedes* mosquitoes.

Control measures aim at killing adult mosquitos using cypermethrine, both indoors and outdoors, through truck-mounted fogging; and killing larvae using *Bacillus thuringiensis israelensis* (*Bti*) liquid* and granulate† applications. Activities are guided by current epidemiology and vector infestation levels monitored in sentinel breeding sites. Municipal vector control teams consist of four to five technicians responsible for a list of potential *Anopheles* breeding sites in their area.

An entomologic map was developed by the Angolan malaria programme in 2012, and a vector assessment was performed in response to a dengue outbreak in 2013. Nevertheless, neither systematic monitoring of *Aedes* infestation levels nor identification of the most productive breeding sites were noted during the assessment visit. In early 2016, *Aedes* control activities were added after rapid entomological assessments in most settings, but without determining the species of the larvae found.

Aedes control is organised as follows:

- Suspected case: inspection of the case's residence and the surrounding homes within a 200 m radius; calculation of larval and adult infestation levels
- Confirmed case: indoor fogging of the case's residence and surrounding homes within a 200 m radius
- Neighbourhoods with a high infestation level: truck-fogging with cypermethrine, door-to-door visits to inspect potential breeding sites, *Bti* application, and informing household members about control measures for *Aedes* control
- In remote areas: fogging of residence and surroundings when a resident returned from Luanda
- information/education/communication messages on household control measures distributed through various channels to achieve community actions
- *Bti* or cypermethrine are not always available because purchase depends on the municipality's priority settings. Application is hampered by the high cost of fuel which needs to be mixed with the adulticide. The municipal vector control teams are often not aware of the main *Aedes* breeding sites or geographical high-risk pockets.

Aedes infestation levels are reaching a Breteau index‡ of 50 to 103 in some geographical pockets while in other areas no *Aedes* mosquitoes were present. Only *Aedes aegypti* has been identified, with neither *Aedes albopictus* nor *Aedes africanus* found. All in all, it remains difficult to determine the geographical distribution of the vector, the corresponding infestation levels, and the entomological risk for local transmission.

Health education, risk communication and social mobilisation

Since the beginning of the epidemic, several communication campaigns in Angola have been conducted using different channels and serving different aims.

Radio, television, the press and flyers carried the message that people with acute fever need to report to the nearest health facility because of a yellow fever outbreak. Information posters in the waiting rooms of health facilities describe yellow fever symptoms and how transmission occurs.

The *Aedes* vector stays in and around houses, hence household members are the main targets for disease prevention and vector control. Door-to-door visits were organised in high-risk zones for vector presence and community mobilisation was organised. Health volunteers (who had already been recruited for other health activities) were trained by municipal vector control workers to pass on messages on breeding site control to the communities.

* The effect lasts about seven days when liquid is used indoors in small containers or 30 days when used in bigger containers for communal settings.
† Effect lasts about 90 days; used in remote areas that are difficult to reach.
‡ Breteau index: the number of water-holding containers positive for (*Aedes*) larvae per 100 inspected homes.

Travel-related measures

The spread of confirmed cases of yellow fever from Angola to other countries has been documented. Imported confirmed cases were identified among returning travellers to China (11), Kenya (2) and the Democratic Republic of the Congo (41). One confirmed case identified in the Democratic Republic of the Congo is reported as having been infected in the Angolan exclave of Cabinda, where no local transmission has yet been reported by the Angolan authorities.

According to the International Health Regulations (IHR), a valid vaccination record is needed to enter Angola. In alignment with this, soon after the beginning of the epidemic, health authorities started to check the vaccination status for individuals entering the country. About 2.7 million passengers per year travel through Luanda International Airport *Aeroporto Internacional Quatro de Fevereiro*.

The following exit and entry regulations are only applied to international flights:

- Upon arrival in Angola, passengers have to produce a valid record of yellow fever vaccination. At the airport, health experts scan for symptomatic travellers. Arriving passengers without a valid vaccination record are vaccinated at the airport free of charge and allowed to enter the country.
  At the time of the visit (12 May 2016), 130 yellow fever vaccine doses were in stock at the airport.
  A vaccination room, a vaccine carrier with cool pack, vaccination records and syringes are available. As of 30 April 2016, 240 Angolan and 276 foreign passengers were vaccinated at the airport. The most frequent countries of departure for travellers vaccinated at the airport from Europe were Portugal (140), France (10), the Netherlands (9), Spain (8) and Germany (5). Countries outside of Europe included Ethiopia (16), China (13), Brazil (11), Vietnam (9) and the Democratic Republic of the Congo (8).
- At the time of departure from Angola, all passengers have to present a valid vaccination record. Those without record, with false records, or those who were vaccinated less than ten days before departure, are denied boarding. Those without vaccination record are offered vaccination at the airport and may depart ten days later. However, these procedures were not enforced on 20 May 2016, when the European Medical Corps were at Luanda Airport to check-in for their flights back to Europe: team members were not asked for proof of yellow fever vaccination, neither at check-in nor before boarding.

In a recent meeting between the MoH in Angola and the international airlines flying in and out from Angola, health authorities requested the companies to ask their passengers for yellow fever vaccination records when boarding flights to and from Angola. Travellers arriving in Angola without a valid vaccination record can be sent back to the country of departure at the expense of the airline company or be vaccinated on the spot. Airlines were preparing for the implementation of the measure at the time of the team mission

The mission team did not visit any sea ports or land border crossings, but according to various sources, vaccination records were not checked at these entry/exist points.

Discussion

The distribution of cases by time of onset shows that the number of newly reported cases has been decreasing slightly since week 15 (10–16 April) of 2016. However, new cases and new areas of local transmission are still being reported, which indicates that the epidemic is not yet under control: at least five provinces show evidence of local transmission in one or more municipalities, and Benguela province continued to show an increasing trend of confirmed cases during the month of April.

Despite a decreasing trend in the number of reported suspected and confirmed cases, the epidemic curve should be interpreted with caution. Case under-ascertainment and underreporting are very likely and have varied over time, which makes it difficult to directly compare case numbers from the different phases of the epidemic. In addition, cases reported for the most recent weeks reflect delays in diagnosis, confirmation and reporting and most likely represent an underestimation of cases.

The difficulties in controlling the outbreak are partly due to the delayed vaccination and vector control measures, which are only implemented after case detection and confirmation of local transmission. The spread of the disease can only be halted through proactive vaccination in urban areas characterised by high population density and intensive human movement, and in areas where the vector is present. The lack of background information on *Aedes* infestation levels and the most productive breeding sites in Angola complicates the planning for vaccination campaigns and efficient proactive vector control. The restricted availability of yellow fever vaccine hampers the possibility of preventing the spread of transmission by vaccinating individuals who live in areas with spots of local transmission.

Severe yellow fever cases can hardly go undetected due to their clinical severity and high case–fatality ratio of about 50%. However, less severe and subclinical infections can easily remain undetected, due to the rather unspecific case presentation and the current health-seeking behaviour (delay, not attending because of drug

shortage in health facilities). Because of the window period between the time of infection and the time when diagnostic tests can detect the disease, cases can stay unconfirmed. A rapid follow-up of suspected cases is therefore imperative.

The limitations of IgM/IgG testing are:

- The cross-reactivity among flaviviruses (including dengue, Zika, Japanese encephalitis, West Nile and yellow fever)
- Challenges to differentiate acute infection from past infections or from vaccination
- The differential presentation of IgM and IgG levels when cases are primary or secondary flavivirus infections
- Shortcomings in the surveillance system in Angola; despite having been strengthened recently and relying on the WHO system established for acute flaccid paralysis surveillance, the system has flaws.

The response strategy faces five main challenges:

- Lack of a uniform definition for suspected cases in the first months of the epidemic
- Changes in the case definition over time, from more sensitive to more specific
- Difficulties with blood sample collection, storage and transport (the situation has recently improved)
- Likely under-ascertainment of yellow fever cases and underreporting of suspected cases from part of the municipalities and provinces
- Underreporting of confirmed cases because suspected cases with only weak evidence of vaccination (self-reporting and no date of vaccination analysis) are automatically added to the category of 'non-confirmed suspected cases'.

The vaccinated proportion of the Angolan population is rapidly increasing. The current mass vaccination campaign is supposed to be completed by the end of May, with about 11.2 million people vaccinated over a period of about four months. In order to meet the objective of vaccinating the national target population, another 7.2 million people would need to be vaccinated. At the current rate, this would take about 80 days. The shortage of vaccine, a major issue in the previous months, was not taken into account for this rough calculation.

In the meantime, transmission is ongoing and could continue for several more weeks. Of particular concern are those areas with high mobility and those where vaccination campaigns have been carried out and local transmission is still ongoing (e.g. municipalities in Luanda province). Furthermore, vaccination coverage is not consistently high in areas where vaccination campaigns took place. There have also been reports that vaccination effectiveness has dropped and that adult males are less likely to get vaccinated. Geographical pockets where transmission is still ongoing exist despite acceptable overall coverage rates: as of 15 May 2016, there are nine municipalities where less than 70% of the target population are vaccinated. Finally, census data, which are used to calculate vaccination coverage, may be imprecise, especially in rapidly growing urban areas like Luanda and other large towns.

The lack of targeted vector control efforts (because of limited data on vector presence and infestation levels, insufficient resources, and irregular availability of insecticides) jeopardizes the efficiency of the ongoing vector control activities.

Threat assessment

Risk of infection in Angola for residents and travellers to Angola

Any unvaccinated traveller or resident in an epidemic area is at risk of being infected. Currently, all regions in Angola should be considered as areas at high risk of transmission of yellow fever. Representatives of EU embassies in Angola reported that more than 95% of all EU citizens in Angola are vaccinated. People who cannot be vaccinated have been a matter of concern, e.g. newborn babies and people with underlying health conditions.

Risk of importation to the EU and of international spread

According to WHO, the worsening situation in Angola is a serious public health event which warrants intensified national action and enhanced international support. On 19 May 2016, a WHO Committee decided that, based on the available information, the event does not at this time constitute a public health emergency of international concern.

The number of yellow fever cases in this large national outbreak is underestimated. Up to 85% of the cases can be asymptomatic but are still able to transmit the virus to the vector. Attendance at health facilities and surveillance is reportedly not optimal. In addition, the region has become well connected, and people frequently travel by road or

plane to neighbouring countries, therefore increasing the risk for exporting the virus to other countries. Imported cases from Angola have already been reported in the Democratic Republic of the Congo (41 confirmed cases), Kenya (2 confirmed cases) and China (11 confirmed cases in returning foreign workers). Viraemic patients travelling to areas where there are suitable vectors and susceptible human populations pose a risk for the establishment of local transmission. Such areas exist in most of the intertropical zones of Africa, the Americas and Asia. Therefore, the risk of international spread is currently high and has already occurred in two different areas of the Democratic Republic of the Congo.

As yellow fever and dengue fever share the same *Aedes aegypti* mosquito vector, area with documented dengue transmission would also be suitable for the establishment of local transmission of yellow fever – if the virus is introduced by a viraemic traveller. This could be the case in southern China, where dengue virus transmission occurs during the warmer mosquito vector season, leading to local outbreaks in these areas. However, it has to be stated that yellow fever has never been transmitted by the local *Aedes* species in south-east Asia [18].

Travellers coming from affected areas may not have been vaccinated against yellow fever and may therefore arrive in the EU/EEA and become viraemic as they develop yellow fever, creating a risk for the potential local transmission of the disease in areas where the vector is present.

The risk of importation of yellow fever into Europe is limited because vaccination status upon exit has not been consistently implemented and proof of yellow fever vaccination is not a requirement to obtain a valid visa to enter the Schengen area.

Risk of spread in the EU

The risk of establishment of yellow fever transmission in the EU/EEA is low, even in areas where *Aedes aegypti* is present. The mosquito is established in the Overseas Countries and Territories and Outermost Regions of the EU, the yellow fever belt (intertropical area), and in the Black Sea region of Europe (http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx).

The vector competence of European *Aedes albopictus* mosquito populations needs to be further assessed, but potential local transmission of yellow fever in areas where *Aedes albopictus* is present in the EU/EEA cannot be ruled out if the virus is introduced by a viraemic traveller.

Conclusions and options for response

Over the last six months, Angola has been experiencing a national yellow fever outbreak. Although the number of new reported cases decreased over the last weeks and a mass vaccination campaign reached about half of the targeted population, the outbreak is still ongoing and not yet under control. Local transmission is reported in many areas of the country and in geographical pockets. Large urban areas and provinces such as Cabinda represent a high risk for international spread: a case identified in the Democratic Republic of the Congo was reportedly infected in Cabinda.

Actions to minimise the risk of infection in Angola for residents and travellers to Angola

Preparedness

Angolan authorities should consider creating a rapid outbreak response team at the national level for the rapid deployment, investigation and control of new clusters or outbreaks.

Angolan authorities should also consider training key health personnel at the national, provincial and municipal levels (health directors, epidemiologists and laboratory technicians) on the main aspects of outbreak prevention and outbreak response. A course in 'Resposta integrada ao surto' was previously available in the country and could be taught again.

Surveillance

Authorities should ensure the consistent use of the case definition at the national level. Ideally, the same definition is used in other affected countries to facilitate cross-border analysis. All cases fitting the case definition should be reported, including those with a history of vaccination and those testing positive for malaria infection. In order to better appreciate the epidemic dynamics, it would be helpful to present the distribution of cases over time in accordance with the case classification system (confirmed cases, suspected cases that tested negative, suspected cases not-tested and suspected cases with a vaccination history).

The algorithm to include or exclude suspected cases based on their vaccination history should be improved. With the increasing vaccination coverage, a substantial proportion of suspected cases is excluded from confirmation on the basis of this criterion, with the risk of excluding actual yellow fever cases. Vaccination history should be based on vaccination records only (not on self-report). The algorithm used by the 'case confirmation committee' to classify cases should be more robust and consistent when considering the time between vaccination and onset of symptoms. This is especially relevant when these dates are very close in time (fewer than 10 days). An epidemic curve based on date of reporting should be produced in addition to those by week of onset, in order to allow for a better understanding of the dynamics of the epidemic in the most recent weeks.

Surveillance should be strengthened at the national level, particularly in areas such as Cabinda province, which has been linked to international cases.

The time needed to report laboratory confirmations from the national to the municipal level should be shortened to one week from sending the samples and receiving the results.

Vaccination

- Accelerated and prioritised vaccination campaigns should be held in municipalities with a highly mobile population and in densely populated urban areas where *Aedes* mosquitoes are present (e.g. Lubango, Huíla province, and Cabinda province).
- Municipalities surrounding areas of local transmission should be prioritised in order to provide a vaccinated buffer zone and prevent the further spread of yellow fever.
- Mop-up campaigns in local transmission areas with low vaccination coverage and new cases should be implemented to prevent transmission in areas previously targeted by vaccination campaigns, e.g. Luanda province. Understanding the reasons for not getting vaccinated can help public health authorities to implement interventions to increase vaccine acceptance.
- Further vaccine supplies are needed to conduct vaccination campaigns in additional municipalities. Vaccinations should also be carried out in urban areas where the vector is present, but local transmission has not yet been confirmed (85% of cases have mild and nonspecific symptoms, which is why many of these cases are overlooked, as are areas of ongoing local transmission). Sufficient yellow fever vaccination stock should be available for routine childhood vaccination.
- In addition to the age group, the gender of all vaccinated persons should be recorded. A few vaccination sites that recorded age were able to document that vaccination coverage among men was clearly lower than among women. Age can be recorded at the entrance of a vaccination site, but also through post-vaccination coverage surveys.
- Waiting times at vaccination sites should be minimised, waiting areas should offer a minimum level of comfort, and sites should have separated entry and exit points.
- Social media campaigns about yellow fever vaccinations and vector control measures should be continued.
- Monitoring of adverse events following immunisation should be implemented during the current vaccination campaign.
- Support and deployment of international human resources could be of benefit to reach a higher vaccination coverage in a shorter time. GOARN (Global Outbreak Alert and Response Network) deployment and international NGOs could offer rapid support in outbreak control activities at the provincial and municipal levels.
- Children below six months of age are at risk of infection and neither targeted by routine nor mass vaccination. These unvaccinated children should be protected against mosquito bites with insecticide-treated mosquito nets.
- Entry into Angola should only be allowed after presenting a valid yellow fever vaccination record in order to protect unvaccinated people and avoid enlarging the group of susceptible people.

Vector control/entomology during the epidemic

As confirmation of cases is often only available after several days, it is essential to ensure that fogging is performed as soon as a suspected case is detected; waiting for case confirmation results in losing valuable time.

Bti and cypermethrine should be made available in all provinces and all municipalities, even if there is no local transmission, so it can immediately be used to prevent transmission as soon as cases are reported. Municipal vector control teams should be kept continuously updated on the neighbourhoods at high risk of transmission and the main breeding sites.

Vector control/entomology post-epidemic

The transmission of arboviruses has been documented several times in Angola (dengue in 2013, chikungunya in 2014 [19], yellow fever in 2016). A thorough entomological characterisation of *Aedes* vectors should be performed, including a description of geographical spread, infestation levels at certain geographic locations (larval and pupal stages, with differentiation of species such as *Aedes aegypti, Aedes albopictus, Culex* and others), identification of

main and most productive breeding sites [20]. Once this information is available, entomological surveillance strategies have to be selected and adapted to the entomological characteristics of the area, e.g. larvitraps if *Aedes* infestation is low [21], sentinel sites, and rapid surveys on *Aedes aegypti* infestation [22]). In addition, the selected control strategies should be clearly defined.

Laboratory capacity and testing

- Laboratory capacities could be improved to reduce the confirmation delay and possibly also perform PCR confirmation at the provincial level. In addition, capacities for virus genotyping could be developed in Angola.
- Laboratory capacities for the differential diagnosis of positive flavivirus IgM samples should be improved to distinguish between acute and past infections:
  - Acute case: NS1 or IgM positive (with or without positive IgG results)
  - Past case: IgG positive
- A subsample of positive and negative samples could be tested for IgG to gain a better understanding of the discriminatory power of IgG testing and whether it should be recommended.

Case management

Case management protocols should be harmonised at the provincial and national levels and include the following:

- A syndromic approach for screening at the emergency department level
- The establishment of clinical standards for the management of suspected cases of yellow fever
- The necessity to confirm yellow fever vaccination history through vaccination records should be emphasised; if no records are available, a person should be considered unvaccinated.
- Healthcare workers should be trained in the management of the diagnosis of yellow fever and the treatment of yellow fever patients
- Regular audit of results should be undertaken; this should include checks that epidemiological records and vaccination dates were properly recorded.
- Auditing all fatal yellow fever deaths for which vaccination was reported.

Actions to minimise the risk of international spread from Angola

- In order to avoid exportation of yellow fever virus to countries, individuals should only be allowed to enter and leave Angola if valid vaccination records are produced. This is in accordance with the International Health Regulations. At the time of writing this assessment, implementation of this strategy is currently absent or performed in a limited way.
- International authorities should consider not issuing visas for travellers from Angola if they cannot provide proof of yellow fever vaccination. In order to harmonise the criteria for the EU Member States, the European Commission should implement a binding regulation on this subject, addressed to all EU embassies in Angola and the countries affected by the ongoing yellow fever outbreak.
- Airlines should only board passengers from Angola with proof of yellow fever vaccination.
- These procedures should also be applied to land and sea borders.
- Outbreaks of yellow fever in urban settings can rapidly spread and lead to a public health emergency requiring mass immunisation campaigns for containment purposes. In the long term, enforcing preventive immunisation through routine childhood vaccination in endemic countries can significantly reduce the burden of the disease.
- Vaccination against yellow fever is recommended for all people aged nine month or older who are travelling to areas where there is evidence of persistent or periodic yellow fever virus transmission. WHO publishes yellow fever vaccination requirements and recommendations in a list of countries, territories and areas [23]. The yellow fever vaccine is recommended for travellers to Angola. The country specifies that a yellow fever vaccination record is required for travellers above the age of nine months. According to the Emergency Committee of the International Health Regulations (advice of 19 May 2016), a yellow fever vaccination certificate will be valid for life.
- To address the current gap between supply and demand of yellow fever vaccine, vaccine production should be scaled up, both for emergency response and routine vaccination programmes.
- Studies assessing the competence of the European *Aedes albopictus* mosquito populations and the capacity to transmit yellow fever should be reviewed.
- Clinicians should consider yellow fever among travellers returning from affected areas. Suspect and confirmed patients should be prevented from being bitten by *Aedes* mosquitoes in areas where they are present (for example through the use of a mosquito net).

Note: There is a sufficient number of EU diagnostic laboratories with the capacity to detect yellow fever.

Research priorities

Although hardly applicable during the current outbreak, the following research topics should be prioritised:

- Rapid and easy-to-use diagnostics for the efficient monitoring of yellow fever outbreaks
- Treatment for yellow fever
- Effective vector control measures
- Virus persistence in infected individuals and IgM and IgG positivity in primary and secondary cases in order to improve case confirmation
- Development of simpler laboratory methods to perform complement fixation tests to differentiate between wild virus and vaccine-derived virus infections in confirmed cases
- Is it possible that yellow fever can be transmitted sexually? If so, the determinants of sexual transmission of yellow fever need to be assessed.
- Development of a non-egg based vaccine

Limitations

This report is mainly based on interviews with local professionals and on information from the field because no raw data were available for analysis. Therefore, quantitative analysis was not possible. All quantitative results and figures in this report rely on analyses provided by the Angolan MoH and WHO.

It was impossible to verify information collected through the surveillance system because the mission team had no access to raw data and databases at the municipal, provincial and national levels. The same applies to all related information collected from institutional and non-institutional partners. The team did not visit private clinics, and information on how private clinics contribute to the national yellow fever surveillance system was contradictory. It was neither an option nor one an objective of this mission to accompany an active case investigation.

The team visited three Angolan provinces (Luanda, Huambo and Huíla), which might not be representative for the whole country. Field visits did not include a province that notified no confirmed cases at all, which would have been helpful in order to determine if appropriate surveillance systems for yellow fever are in place.

Furthermore, no field visits to the exclave of Cabinda were possible. Cabinda is in a risk-strategic position in this outbreak, bordering the Democratic Republic of the Congo and the Republic of the Congo. It also has strong ties to the cities of Pointe-Noire, Kinshasa and Brazzaville, and the oil industry.

Annex

Table 1. Yellow fever vaccination in Angolan provinces, overview, as of 20 May 2016

Distribution of confirmed cases, population figures, start date, status of the vaccination campaign, number of administered vaccinations, and vaccination coverage by province and municipality

Province	Municipalities and districts	Confirmed cases	Vaccination campaign				
			Population estimates[1]	Start date	Status	Administered doses	Vaccination coverage
Luanda	Cazenga	103	867 659	29 Feb 2016	Completed	806 016	93%
	Viana	93	1 535 102	02 Feb 2016	Completed	2 117 757	138%
	Cacuaco	75	887 829	29 Feb 2016	Completed	767 241	86%
	K. Kiaxi	59	640 006	10 Mar 2016	Completed	209 356	33%
	Belas	50	1 071 662	19 Feb 2016	Completed	1 287 615	120%
	Sambizanga	29	433 970	20 Mar 2016	Completed	133 146	31%
	Maianga	26	660 884	14 Mar 2016	Completed	478 869	72%
	Rangel	14	136 031	28 Mar 2016	Completed	40 156	30%
	Ingombota	4	89 556	24 Mar 2016	Completed	60 103	67%
	Samba	4	160 174	24 Mar 2016	Completed	49 345	31%
	Icolo e Bengo	1	75 103	28 Mar 2016	Completed	31 642	42%
	Kissama	1	25 240	28 Mar 2016	Completed	13 774	55%
Benguela	Baia Farta	7	103 623	16 May 2016	Ongoing		
	Balombo	4	99 932	16 May 2016	Ongoing		
	Benguela	27	531 744	12 Apr 2016 16 May 2016	Ongoing	375 732	71%
	Caimbambo	1	81 212				
	Catumbela	2	173 601	13 Apr 2016	Completed	188 440	109%
	Chongoroi	4	81 977				
	Cubal	3	289 703	16 May 2016	Ongoing		
	Ganda	3	226 051				
	Lobito	13	335 601	13 Apr 2016	Completed	355 367	106%
Huambo	Bailundo	11	283 887	16 May 2016	Ongoing		
	Caala	24	268 734	13 Apr 2016		222 811	83%
	Catchiungo	2	116 334				
	Ekunha	17	79 334	15 May 2016	Ongoing		
	Huambo	39	689 301	13 Apr 2016	Completed	558 150	81%
	Londuimbali	7	125 214				
	Longonjo	10	87 329				
	Mungo	2	111 109				
	Tchikala	3	102 541				
	Tchindjendje	1	28 371				
	Ukuma	4	42 950	15 May 2016	Ongoing		
Kuanza Sul	Amboim	2	236 339	16 May 2016	Ongoing		
	Cassongue	2	141 452	16 May 2016	Ongoing		
	Cela	1	219 850				
	Ebo	4	159 024	16 May 2016	Ongoing		
	Libolo	1	85 630	16 May 2016	Ongoing		
	Seles	3	176 058	16 May 2016	Ongoing		
	Sumbe	1	269 341				
Huíla	Caconda	10	160 892	17 May 2016	Ongoing		
	Cacula	2	129 201				
	Caluquembe	2	170 463				
	Chibia	1	182 548				
	Chicomba	1	128 056				
	Gambos	1	76 456				
	Humpata	3	83 267				
	Lubango	4	736 077				
	Quilengues	4	69 105				
	Quipungo	3	147 818	16 May 2016	Ongoing		
Uige	Bembe	1	32 337				
	Negage	2	136 323	16 May 2016	Ongoing		
	Uige	4	496 567	16 May 2016	Ongoing		
Total			**14 278 568**			**7 695 520**	

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