

Emerging infectious diseases in Africa in the 21st century

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Abstract

Many infectious diseases have emerged or reemerged in Africa in the 21st century. Some of them are associated with newly discovered microorganisms such as *Rickettsia felis* and *Tropheryma whipplei*; others are known, historical diseases such as plague and cholera. In addition are diseases related to previously known microorganisms which recently have been involved for the first time in massive outbreaks with worldwide impacts (such as Ebola virus, Zika virus and Chikungunya virus). Research on emerging infectious diseases needs to be identified as a priority.

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Keywords: Africa, cholera, emerging infectious diseases, fever, plague

Original Submission: 9 March 2018; **Revised Submission:** 29 August 2018; **Accepted:** 6 September 2018

Article published online: 21 September 2018

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At the beginning of the 21st century, infectious diseases remain responsible for about one quarter of deaths worldwide, causing at least 10 million deaths per year, mainly in the tropical countries [1,2]. Emerging infectious diseases are a high burden on public health but have also an impact on global economies [3]. Their origin is generally connected to social and economic conditions as well as environmental and ecologic factors [3]. A substantial risk of wildlife zoonotic and vector-borne emerging infectious diseases exists mainly at lower-latitude developing countries such as tropical Africa [3]. Overall, 60% of emerging infectious diseases are zoonoses, of which 72% are from wildlife [3].

Emerging infectious diseases are mainly those that have recently appeared in a population or have already existed but are rapidly increasing in incidence or geographic range [4]. Although much depends on the type of emerging infection, the development of modern rapid, sensitive and accurate methods of microorganism detection has played an important role in the diagnosis and identification of emerging infectious diseases, such

as for the molecular detection of *Rickettsia felis* and *Tropheryma whipplei*.

Several factors of emergence have been identified: microbial adaptation and change, human susceptibility to infection, climate and weather, changing ecosystems, human demographics and behavior, economic development and land use, international travel and commerce, technology and industry, breakdown of public health measures, poverty and social inequality, war and famine, lack of political will and intent to harm [5]. Unfortunately, most of these factors are over-represented in many countries of Africa. Thus, many emerging diseases are reported from or originated from Africa. Among the most important are HIV infection and malaria, which emerged from wild monkeys [6]. Finally, improved disease assessment through improved public health surveillance could also contribute to the apparent onset and reappearance of some diseases.

Here we briefly describe new diseases and emerging or reemerging known diseases that have been involved in outbreaks since the beginning of the 21st century in Africa. Although most are zoonotic, some of them, such as *T. whipplei* infections, cholera and measles, do not have a zoonotic component.

Africa can be seen as distinct from the rest of the world, and even from other parts of the developing world which are also affected by the emergence and reemergence of diseases. Most

dangerous infectious agents that kill humans originate in Africa. In addition, the difficulties with morbidity surveillance in Africa are well known. In the context of the multiple epidemics that have been recognized over the past decade, numerous assessments of surveillance systems have revealed problems essentially across the board [7]. Poverty and poor healthcare exacerbate health problems. African countries rank among the lowest in per-capita spending on health and the availability of physicians. According to the Worldwatch Institute (<http://www.worldwatch.org>), in 2001 an average of \$36 per person was spent on healthcare in Africa. The spending amounted only \$6 in Niger, \$7 in Sierra Leone and \$15 in Nigeria compared to \$4800 in the United States. Moreover, 32% of the population is

undernourished; five of the six worst countries for mortality of children under 5 years are in Africa, with an under-5 mortality rate above 100 deaths per 1000 live births, according to the World Health Organization. Half of all deaths in Africa are caused by infectious diseases, compared to only 2% in Europe. This means that Africa should be the number one priority in the world community's struggle against infectious diseases. Surveillance of emerging infectious diseases is vital for the early identification of public health threats.

Rickettsia felis was reported for the first time in the United States and was officially described in 2002. Before 2010, the bacterium was mainly found in arthropods, especially in cat fleas, *Ctenocephalides felis*, with a worldwide distribution. It was

TABLE 1. Emerging and reemerging bacterial diseases in Africa in 21st century

Bacteria	Implications for Africa	Targets for prevention	References
<i>Rickettsia felis</i>	<ul style="list-style-type: none"> • 2002: Officially described • Before 2010: Only one case reported in Africa • 2010: Prevalence of about 4% of <i>R. felis</i> in blood samples of febrile individuals without malaria in Senegal (9/204) and Kenya (6/163) • 2013: Confirmation of role of <i>R. felis</i> in fever in Senegal • 2015: First detection in blood samples of febrile individuals in Gabon, reaching a prevalence of 39.7% (23/58) in rural area of Fougamou 	Vector-control measures	[8–10,13]
<i>Tropheryma whipplei</i>	<ul style="list-style-type: none"> • 2001: Officially described • 2010: (a) Prevalence of about 6.4% (13/204) in blood samples of febrile individuals without malaria in Senegal; (b) Main detected cause of fever in Sine-Saloum area in Senegal, in August 2010 (prevalence of 58.5% [17/29] in febrile individuals in village of Dielmo and 69% [9/13] in those of Ndiop) • 2016: First detection in a febrile patient in Gabon 	Sanitation facilities	[22,26,56]
<i>Yersinia pestis</i> (plague)	<ul style="list-style-type: none"> • Since 2000: Main outbreaks: Recurrent annual human infections and outbreaks in Madagascar, DRC, Uganda, United Republic of Tanzania (2000) • DRC, Uganda, United Republic of Tanzania (2001) • DRC, Malawi, Mozambique, Uganda, United Republic of Tanzania (2002) • Algeria, DRC, Mozambique, Uganda (2003) • DRC (2005) • DRC (2006) • Madagascar (2017): One of worst outbreak in world in past half century, 202 deaths 	Reduce risk of wildlife-to-human transmission	[29], http://www.who.int/csr/don/27-november-2017-plague-madagascar/en/
<i>Vibrio cholera</i> (cholera)	<ul style="list-style-type: none"> • Main outbreaks since 2000: • Madagascar, Somalia (2000) • South Africa (2000–2001) • Chad, Nigeria, Tanzania, West Africa (2001) • Burundi, Côte d'Ivoire, DRC, Liberia, Malawi, Niger (2002) • Mozambique (2002–2004): 17 265 cases, 102 deaths • Benin, Côte d'Ivoire, DRC, Liberia, Mali, South Africa, Uganda, Zambia (2003) • Cameroon, Chad, Zambia (2004) • Niger (2004–2005) • West Africa (2005) • Angola and Republic of South Sudan (2006) • West Africa (2008) • Zimbabwe (2008–2009): largest outbreak, 98 585 cases, 4000 deaths • Zimbabwe (2011) • Central Africa, DRC, Sierra Leone, Republic of the Congo (2012) • Republic of South Sudan (2014) • DRC (2015) • United Republic of Tanzania (2015–2018): 33 421 cases, 542 deaths • Kenya, Zambia (2017) • DRC, Mozambique, Somalia (2017–2018) • Algeria (2018): Since mid-August 2018, 41 confirmed cases, two deaths, last reported sporadic cases in 1996 in this country (data provided by Algerian health authorities) 	Appropriate water and sanitation facilities Oral cholera vaccination (transient protection about 3–5 years) To be alert during conflicts or natural disasters	[32,33], http://www.who.int/csr/don/archive/disease/cholera/en/

DRC, Democratic Republic of the Congo.

also considered as a rare cause of rickettsial spotted fever transmitted by fleas. Only about 70 described human cases of infection due to *R. felis* have been reported. In 2010, two studies conducted in Senegal and Kenya by two independent teams showed a prevalence of about 4% of *R. felis* DNA in blood samples of febrile individuals without malaria (Table 1) [8,9]. A more consistent study, involving 2024 febrile and 391 afebrile subjects, confirmed the role of *R. felis* in fever in Senegal [10]. *R. felis* was also detected in eschar samples (5/68, 7.4%) and skin swabs (3/60, 5%) from healthy Senegalese villagers [11]. The presence of *R. felis* was also observed in faecal samples from Senegalese villagers (8/451) [12]. In Gabon, *R. felis* was detected in blood samples of febrile patients, reaching a prevalence of 39.7% in the rural area of Fougamou [13]. The bacterium was also detected in the rural area of Lastourville (11.2%) and, less frequently, in the city areas of Koulamoutou (2.1%) and Franceville (1.3%) [3,14]. Overall, *R. felis* is commonly detected in febrile patients in sub-Saharan Africa. *R. felis* is also usually detected in cat fleas, although not in Senegal [15]. *Anopheles gambiae* mosquitoes are suspected to transmit the bacterium; this was strongly supported by a recent experimental model [16,17]. *R. felis* was also detected in a nonhaematophagous ubiquitous household pest, the booklouse *Liposcelis bostrychophila*, which also may play a role in the *R. felis* transmission [18]. However, an experimental model remained to be developed to better determine its role. Moreover, the omnipresence of *L. bostrychophila* in households and its 100% level of *R. felis* infection may explain the occasional detection of *R. felis* on healthy skin [11]. Other rickettsial diseases also may be considered to be neglected and emerging diseases in Africa [19]: African tick-bite fever is more frequently being diagnosed among travellers returning from Africa [20].

Tropheryma whippelii is the agent of Whipple disease, a chronic disease mainly observed in white men about 50 years old. The disease was first described in 1907, but the bacterium was cultured only in 2000 [21,22]. The high prevalence of asymptomatic carriage of *T. whippelii* in feces and saliva was reported in 2008 in Senegal [23] and in 2016 in Ghana [24]. *T. whippelii* was also detected in the blood of febrile Senegalese patients without malaria, with a prevalence of 6.4% (Table 1) [21]. No correlation was reported between the presence of *T. whippelii* in stool and saliva and bacteraemia, but the presence of one significant clinical sign, cough, was observed. *T. whippelii* was also found in important quantities in bronchoalveolar lavage samples in Malawi [25]. In the Sine-Saloum area in Senegal in August 2010, *T. whippelii* was the main detected cause of fever (58.5% in febrile patients in the village of Dielmo and 69% in Ndiop) [26]. Most of the cases were grouped in the same households. In addition, the same new *T. whippelii* genotype was detected among patients. Overall, the data show that *T. whippelii* is a cause of epidemic

acute fever in Senegal. The examples of *R. felis* and *T. whippelii* support the notion that malaria in people with undifferentiated fever has long been overdiagnosed. They also show that diagnostic tests are essential to improve care, and that targeted surveys have a role to play in providing insight into the causes of the fever in order to suggest the tests to be performed.

Plague has a remarkable place in history. *Yersinia pestis* has been involved in several pandemics. It is present as a permanent focus in many countries in Africa and is still involved in epidemics (Table 1) [27]. Among recent examples, an epidemic of bubonic plague emerged in Oran (Algeria) in June 2003 [28]. The last human cases of plague had occurred in this city in 1946 and in this country in 1950. More recently, in the central highlands of Madagascar, a man visiting Ankazobe district was bitten by a flea in August 2017 [29]. Within a week, he developed malaria-like symptoms. While travelling to the eastern coast, he took a public taxi to reach the capital, where he died. A week later, an epidemic was officially confirmed. The infection of more than 2348 confirmed, probable and suspected cases was reported in November 2017. Although the disease can be treated with antibiotics if detected early, it is worth noting that more than 200 people have died [29]. Overall, the fact that there was a plague outbreak in Madagascar is not astonishing. Indeed, there is an ongoing epizootic that leads to an annual emergence of human infections [29]. This emergence is attributed to seasonal ecologic conditions that cause a decrease in rat populations and then lead fleas to feed directly on humans. The surprising features of this 2017 epidemic are that it appeared earlier than normal; it was predominantly a pneumonic form; and it hit the capital [29]. It is not just bad luck that this plague outbreak emerged in a country with an extremely fragile health system [29]. Indeed, poor access to healthcare, the lack of rapid diagnostic tests in many health facilities, the missing link between communities and the front-line health system and national health authorities as well as weakness of supply chains and infrastructure throughout the country are all factors that favour the spread of the bacterium, resulting in a high mortality rate from a treatable disease [29].

Cholera, caused by the bacterium *Vibrio cholerae*, is re-emerging in Africa as a result of limited access to drinking water and conflicts. Overpopulation, poverty, lack of hygiene, poor sanitation facilities, contamination of food and lack of safe water are the main risk factors for cholera [30,31]. All these elements are also among the consequences of war and civil strife. In 2006, cholera was reported in 33 African countries; 88% of reports came from conflict-affected countries [31]. Cholera epidemics occur almost every year in Africa (Table 1). The most severe outbreak of cholera was observed in Zimbabwe, with 98 585 reported cases including more than 4000 deaths from 2008 to 2009 [32,33].

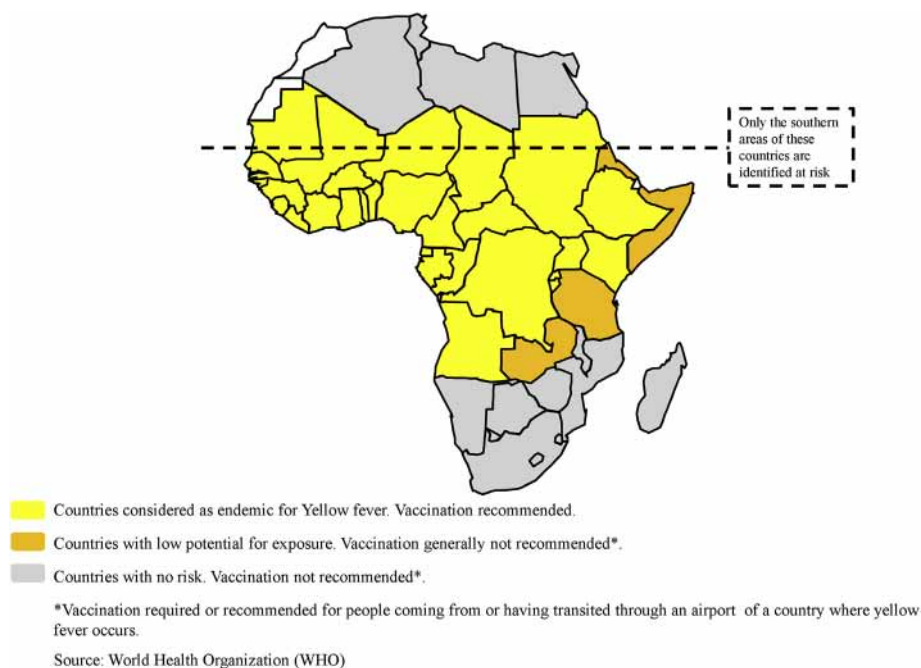


FIG. 1. Yellow fever risks in Africa and vaccination recommendations.

Although mortality from measles has declined in sub-Saharan Africa, it remains a major public health problem in numerous countries like the Democratic Republic of the Congo (DRC), with 294 455 cases including 5045 deaths reported between 2010 and 2013 [33–35]. A total of 186 178 patients (63%) were younger than 5 years old. After the first mass vaccination campaigns, weekly reported cases decreased by 21.5%. However, results of postvaccination campaign coverage surveys indicated suboptimal (less than 95%) vaccination coverage among children surveyed.

Yellow fever virus is a mosquito-borne *Flavivirus* (family *Flaviviridae*) causing infection in humans, with symptoms ranging from mild nonspecific illness to severe disease with jaundice, haemorrhage and death [36]. A single-dose vaccine has been available since the 1940s. It has allowed virus transmission to be controlled and substantially reduced. However, the sylvatic cycle of the virus prevents its eradication. In this sylvatic cycle, nonhuman primates act as primary hosts, and *Aedes aegypti* mosquitoes are responsible for transmission to people. Lack or intermittence of vaccination campaigns, mainly in low-income and/or politically unstable countries, is another factor that can explain the failure to eradicate yellow fever in Africa (Fig. 1) [37]. Since 2000, numerous outbreaks of yellow fever have been observed in West Africa, the Horn of Africa and east-central Africa (Table 2) [36]. Since 2008, an increased number of cases have been also reported in Central African countries, raising the question of whether these reports were related to better surveillance or a real increase in disease [36].

A large epidemic of yellow fever was reported in Angola and the DRC from 2015 to 2016, with 7334 suspected cases [33,38]. Finally, regardless of the cause of the uptick in reports (surveillance improvements or epidemic), the root cause remains the same: a lack of sustained vaccination in the human population.

Monkeypox is a zoonotic disease caused by *Orthopoxvirus*, a virus very close to that causing smallpox in humans. This virus is endemic to central and western African countries. It was first identified in 1958 as a pathogen of *Macaca cynomolgus* (then in use as laboratory animals) and then in 1970 was described as a human pathogen in DRC [39]. The virus is capable of infecting humans, other primates and rodents. Most of the reported cases were related to animal-to-human transmission and were associated with the handling and eating of infected animals, but several cases of human-to-human transmission occurred [40]. Since 2000, human monkeypox cases have been reported in the Central African Republic, Republic of the Congo, DRC, South Sudan, Nigeria, Liberia and Sierra Leone [41,42]. In 2017, Nigeria experienced the largest documented outbreak around 40 years after the last confirmed cases of monkeypox [43].

Ebola fever due to Ebola virus (*Filoviridae*) has caused severe human epidemics identified since 1976. The transmission from animal reservoirs to humans likely happens via direct contact with ill, dead or killed wild animals mainly collected as bushmeat. The virus then spreads in the human population through human-to-human transmission. Since 2001, the disease re-emerged in the forest zone between Gabon and Republic of the

TABLE 2. Emerging and reemerging viral diseases in Africa in 21st century

Viral diseases	Implications for Africa: Main outbreaks since 2000	Targets for prevention	References
Measles	<ul style="list-style-type: none"> Measles outbreaks occur every year throughout Africa DRC (2010–2013): largest outbreak, 294 455 cases, 5045 deaths 	Sustained vaccination in human population	http://www.who.int/immunization/monitoring_surveillance/burden/vpd/monitoring_surveillance_type/Country_slides_measles.pdf?ua=1 [33,36,38], http://www.who.int/csr/don/archive/disease/yellow_fever/en/
Yellow fever virus	<ul style="list-style-type: none"> Nigeria (2000) Guinea, Liberia (2000–2001) Côte d'Ivoire (2001–2003) Senegal (2002–2003) Ghana, Guinea, Republic of South Sudan, Sierra Leone (2003) Burkina Faso, Liberia, Mali (2004) Burkina Faso, Côte d'Ivoire, Guinea, Republic of South Sudan, Senegal (2005) Côte d'Ivoire, Senegal, Togo (2006) Burkina Faso, Central African Republic, Guinea, Liberia (2008) Central African Republic, Guinea, Sierra Leone (2009) Côte d'Ivoire, DRC, Uganda (2010) Côte d'Ivoire, Senegal, Sierra Leone, Uganda (2011) Ghana (2012) Cameroon, Republic of South Sudan (2012–2013) Chad, DRC, Ethiopia (2013) DRC (2014) Angola and DRC (2015–2016): 7334 suspected cases, 962 cases confirmed (393 deaths) Uganda (2016) Nigeria (2017) 	Sustained vaccination in human population	
Monkeypox	<ul style="list-style-type: none"> Central African Republic (2015–2016): 13 cases, fatality rate of 67% among children aged <10 years Nigeria (2017): 146 suspected cases and 42 laboratory-confirmed cases, with death of confirmed monkeypox patient with history of immunosuppression 	Reduce risk of wildlife-to-human transmission	[42,43]
Ebola	<ul style="list-style-type: none"> Gabon and Republic of the Congo (2001–2003) Uganda (2007) DRC (2007, 2008–09, 2012, 2014, 2017) Guinea, Sierra Leone, Liberia (2013–2016): largest outbreak, 28 646 cases including 11 323 deaths DRC 2018: <ul style="list-style-type: none"> Équateur Province (northwest of DRC), 8 May–25 July 2018: 38 confirmed cases, 17 deaths; seven cases were healthcare workers, two of whom died North Kivu Province (eastern DRC), 1 August 2018—ongoing: as of 25 August 2018, 79 confirmed cases, 42 deaths 	Reduce risk of wildlife-to-human transmission	[44–46], http://www.who.int/csr/don/archive/country/cod/en/
Rift Valley fever	<ul style="list-style-type: none"> Egypt (2003) Kenya and Somalia (2006–2007) Sudan and Tanzania (2007) Madagascar (2008–2009) Republic of South Africa (2010) Republic of Mauritania (2016) Republic of Niger (2016) 	Sustained vaccination in animals; vector-control measures	[47], http://www.who.int/news-room/fact-sheets/detail/rift-valley-fever
Zika virus	<ul style="list-style-type: none"> First outbreak detected: Cabo Verde (2015) 	Vector-control measures	[48]
Chikungunya virus	<ul style="list-style-type: none"> Kenya (2004): largest outbreak (almost half a million) Several outbreaks in Guinea, Tanzania, Sudan, Gabon and Cameroon (2004–2007) DRC (2011) 	Vector-control measures	[50]

DRC, Democratic Republic of the Congo.

Congo, in Uganda and the DRC [44,45]. The world's largest ever outbreak of Ebola fever probably started in December 2013 in rural Guinea after the infection of the suspected index case, a 2-year-old child [46]. The subsequent epidemic crossed into Sierra Leone and Liberia [33]. Case numbers escalated quickly [33,46]. Overall, 881 healthcare workers were also infected, and 513 of them died (<https://www.cdc.gov/vhf/ebola/pdf/impact-ebola-healthcare.pdf>). In central Africa, the outbreaks were rural epidemics that occurred in remote locations and involved relatively small case numbers, thus allowing

targeted intervention in the affected villages, whereas the West African epidemic was an urban epidemic that occurred in a highly mobile population, leading to rapid spread of the virus. In DRC, new outbreaks still occur regularly (Table 2), such as the two declared in 2018.

Rift Valley fever is an acute fever most commonly observed in domesticated animals (such as goats, sheep, cattle, buffalo and camels) caused by a virus, a member of the genus *Phlebovirus* (family *Bunyaviridae*), with the ability to infect and cause illness in humans. The virus was first reported in livestock by

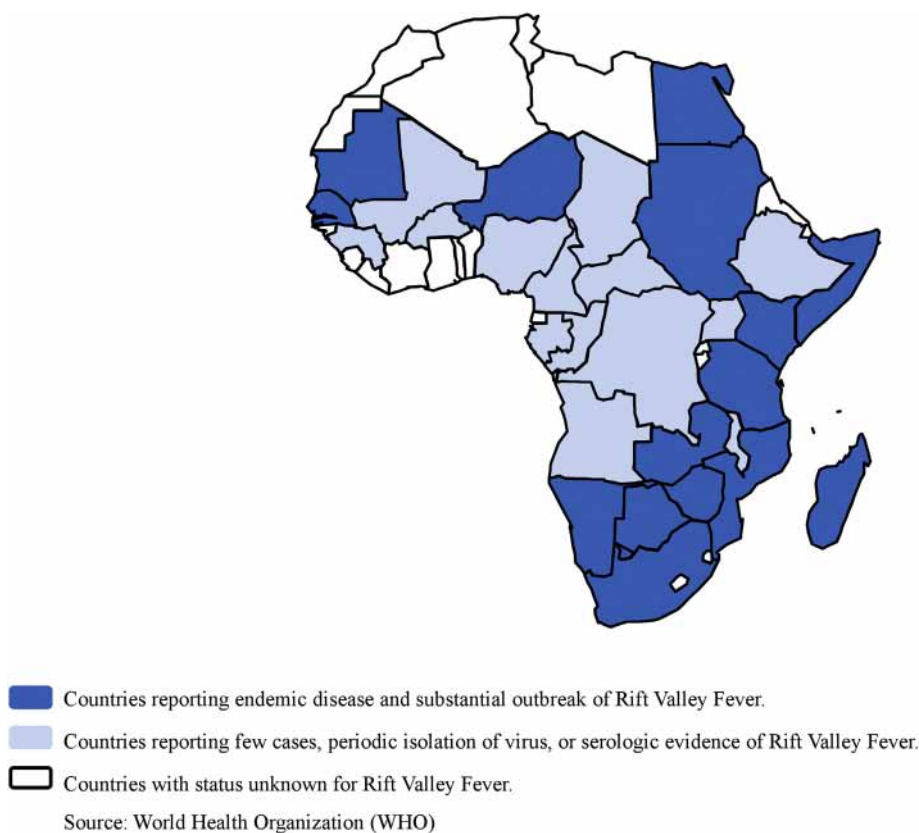


FIG. 2. Rift Valley Fever risks in Africa.

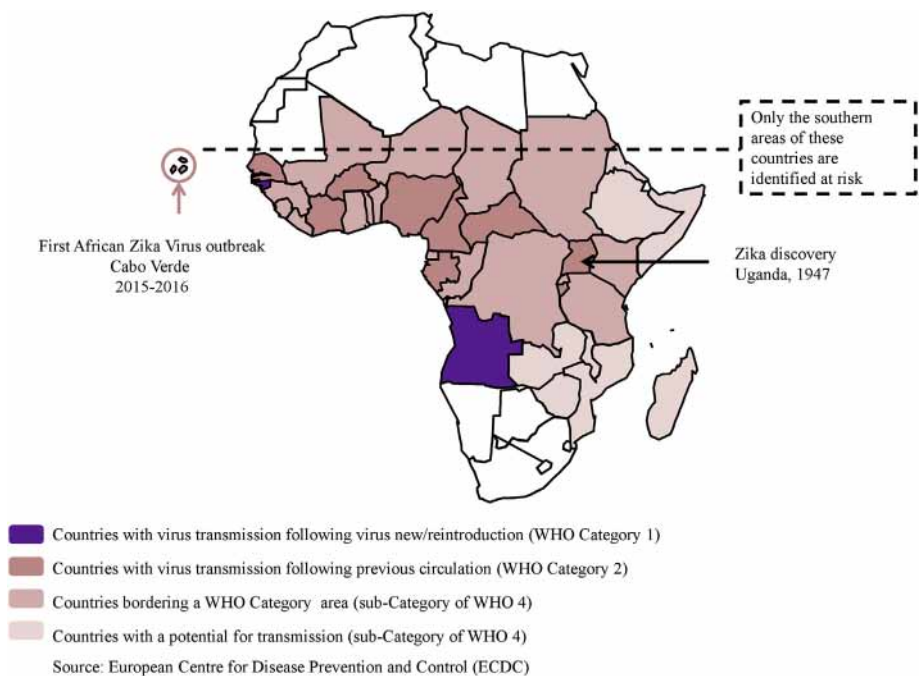


FIG. 3. Zika virus risks in Africa.

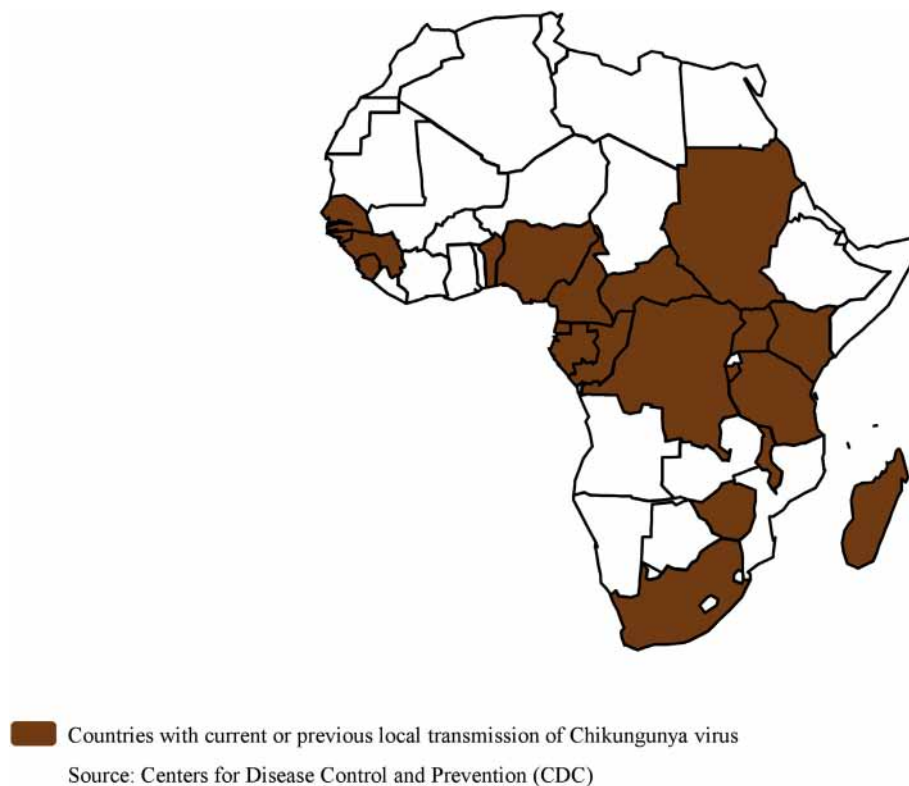


FIG. 4. Chikungunya virus risks in Africa.

veterinary officers in Kenya's Rift Valley in the early 1910s. Rift Valley fever is endemic in several African countries (Fig. 2). Human outbreaks also regularly occur in Africa (Table 2). The two largest outbreaks were those observed in Sudan, with a suspicion of 75 000 human cases and a total of 747 confirmed human cases including 230 deaths, and in Kenya, with a total of 684 cases including 234 deaths (<http://www.who.int/news-room/fact-sheets/detail/rift-valley-fever>) [47].

Zika virus is another *Flavivirus* (family *Flaviridae*) transmitted by *Aedes* mosquitoes. The virus was first detected in April 1947 in a febrile sentinel rhesus macaque monkey in the Zika forest on the shores of Lake Victoria (Uganda) [48]. The first human case was diagnosed in 1962–1963 in Uganda. Overall, data currently support a silent transmission of Zika virus among humans, mosquitoes and animals throughout tropical Africa for more than 70 years without reports of epidemic [48]. In 2007, the first epidemic occurred in the Pacific (Yap Island, Micronesia). The second epidemic affected Polynesia in 2013. The first outbreak of Zika virus in Africa was detected in 2015 in Cabo Verde (Fig. 3). Zika virus exhibited two unique features among the arboviruses: sexual transmission and congenital central nervous system malformations [48]. Sexual transmission was first suspected in an American citizen returning from Senegal and then was confirmed after its emergence in the Americas [48]. The link between Zika virus and severe

malformations of the central nervous system (particularly microcephaly) has been demonstrated by many studies in Brazil and has been reported retrospectively in French Polynesia [48]. Genetic differences between African and Asian/American strains of Zika virus and appearance of the 'pathogenic clone' may explain the emergence of Zika virus infections in South America and Asia [48,49].

Chikungunya virus, an *Alphavirus* (family *Togaviridae*), first reported in Tanzania in 1952, is transmitted by *Aedes* mosquitoes [50,51]. The virus is associated with fever with rash and arthralgias [52]. Severe joint pains can persist for a long time. From 1960 to 1990, epidemics were recorded in the DRC, Central African Republic, Malawi, Uganda, Burundi, Angola, Guinea, South Africa and Nigeria. In 2004, a large epidemic involving almost half a million cases was reported in Kenya [50]. Then this epidemic reached the southwestern Indian Ocean region, India and Southeast Asia [50,51]. From 2004 to 2007, several outbreaks were reported in Guinea, Tanzania, Sudan, Gabon and Cameroon. Two outbreaks were also reported on La Réunion Island in 2009 and 2010 [50]. In 2011, an epidemic hit the DRC [50]. The circulation of chikungunya was also reported in Senegal in the area of Kédougou in 2015 (Fig. 4).

Many other diseases deserve to be mentioned here. Among the most remarkable is the emergence (since 2001–2002) of recombinant poliovirus strains between vaccine strains and

circulating enterovirus strains. These strains derived from oral vaccination rendering poliomyelitis eradication strategies more complex [53]. Tick-borne relapsing fever, although it always existed in Western and Eastern Africa, seems to be reemerging, although this is likely the result of the growing availability of diagnostic methods in rural Africa. Indeed, relapsing fever may be the second leading cause, after malaria, of acute febrile illnesses in rural West African countries such as Senegal [54].

In conclusion, increasing efforts targeting infectious disease studies in Africa have identified new infectious agents. It concerns not only bacterial and viral diseases but also protozoal and helminthic ones. For instance, a new genetic variant of *Mansonella* associated with fever in children was recently reported from Gabon [55]. It is evident that Africa is characterized by the greatest infectious disease burden as well as by the weakest public health infrastructure in the world; further, efforts to establish public health infrastructures that are actually effective may take a period of years, even decades. Emerging infectious diseases should be identified as priority diseases. The challenge will be to combine surveillance and epidemic preparedness and response activities for these priority diseases. Evidently this task is quite difficult because the infrastructure and level of support for surveillance, research and training on emerging infectious diseases in Africa are limited. Laboratory-based surveillance and targeted research surveys to identify common sources of infection in different community types would allow a unified approach to target this enormous challenge. We are persuaded that the most important step towards the elimination of existing burden of infectious diseases in Africa is a massive increase in the number of qualified personnel, including both physicians and scientists.

Conflict of interest

This study was supported by the Institut Hospitalo-Universitaire (IHU) Méditerranée Infection, the National Research Agency under the program « Investissements d'avenir », reference ANR-10-IAHU-03, the Région Provence Alpes Côte d'Azur and European funding FEDER PRIMI.

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