Chapter 2
The Epidemiology

Abstract ZKV was first described in Uganda in 1947. It was isolated from the blood of a Rhesus monkey from the Zika Forest, during a yellow fever study and afterwards in 1948, it was also isolated from multiple *Aedes africanus* from the same forest. Human illness was first described in 1954, in the context of yellow fever outbreak in Nigeria. Since then, very few cases had been described in literature until 2007, when a ZIKV outbreak in Yap Island (Federated States of Micronesia) affected an estimated number of 5000 patients among the population older than 3 years. In the following years, until 2012, sporadic cases were described in some countries in Africa and Asia. In 2013, a new outbreak in Pacific Islands was estimated to affect over 30,000 people and implied an increasing number of neurological complications like Guillain–Barré syndrome (GBS). Also, in 2014 the first confirmation of the potential ZKV sexual transmission (ZIKV was isolated in a semen sample) and the first vertical transmission cases were described. In March 2015, the first ZIKV cases in America during an outbreak of exanthematous illness in Brazil (Bahia) were confirmed. During which ZIKV cases have been reported in other American and Caribbean countries and territories, with a continuous geographical expansion. At the same time, an increasing number of microcephaly and other central nervous system syndromes in newborns and GBS cases in most of these countries have been reported. On 1 February 2016, World Health Organization (WHO) declared Public Health Emergency of International Concern (PHEIC), the potential link with ZIKV infection and the microcephaly and other neurologic syndromes cases. So far, 25 countries from Americas, Africa and Asia had notified confirmed autochthonous ZIKV cases and additional seven countries have reported ongoing outbreaks of ZIKV infection.

2.1 Historical Outbreaks

Zika virus (ZIKV) was first isolated in 1947, from a sample of blood of a Rhesus monkey in Zika Forest, Uganda [1]. The next year, it was described in multiple *Aedes africanus* that could infect mices, monkeys and others mammalians. At that

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time, it wasn't clear if it can produce clinical disease or latent infection in humans, given that it was demonstrated ZIKV seroprevalence of 6,1% in 99 sera tested [2].

The first ZIKV illness in humans was described in 1954 in three patients during an outbreak of yellow fever in Nigeria. One of these patients was diagnosed by isolation of the virus and the other two by a rise of serum antibodies. All of them complained of fever, but only one of them was associated with jaundice [3].

During the next 50 years (until the first important ZIKV outbreak in Micronesia in 2007), there is very limited data about this concern, despite it is widely known that ZIKV main vector (*Aedes aegypti* and *albopictus*) has a worldwide presence including Africa, Asia and America [4]. In a systematic review of the published literature about ZIKV seroprevalence from 1947 to 2007, it was found that ZKV has been endemic for years in sub-Saharan Africa and Asia with an upwards seroprevalence of 50%, and 15–40% among reproductive ages [5]. But only nine cases of clinical infections, with natural transmission and confirmed virus isolation, had been described from 1954 to 2007 [3, 6–9]. Figure 2.1 shows the seropositive identification during this period of time by a systematic review of literature [5].

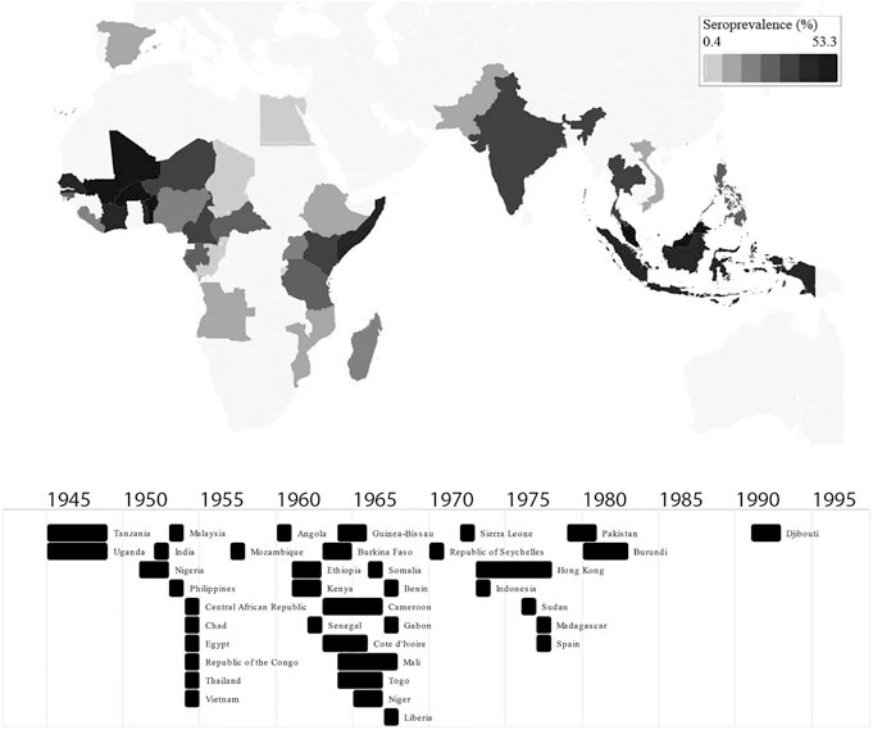

Fig. 2.1 *Above* ZIKV seroprevalence in countries up to April 2007. *Down* First years of identification of ZIKV seropositivity by country [5]

Molecular studies were carried out from 1968 to 2002 with samples of ZIKV isolated in Africa in eight countries, which map the disease as it moves during the twentieth century, from Uganda to western Africa and Asia [10].

Multiple hypotheses have been made trying to explain that period with under-reported and misdiagnosed cases of ZIKV infection. On the one hand, the high prevalence of subclinical infections and the similarity of symptoms with other arboviral infections that are endemics in the same geography could partially explain this fact [11].

Fist important outbreak of ZIKV was reported in April and May 2007, when an illness characterized by subjective fever, arthralgia, conjunctivitis and rash was estimated to affect at 73% (5000 infections) of population older than 3 years in Yap Island (Federated States of Micronesia). There were neither hospitalizations, hemorrhagic complications, nor deaths associated [12].

In 2008, while working in Senegal, two American scientists contracted ZIKV infection and one of them transmitted it to his wife, suggesting the first sexual transmitted infection of ZIKV described in an infection usually transmitted by mosquito bites [13].

Sporadic cases were described in the following years until 2013–14 in Cambodia, Cameroon, [11] Thailand [14], and characterization of strains of all cases described with a virus isolation was performed. Phylogenetic trees were constricted and two geographically lineages were identified: African and Asian. Findings in ZIKV strain isolation during the Micronesia outbreak suggested that it was initiated by a Southeast Asia strain [11, 15].

A new outbreak of ZIKV Asian lineage occurred in October 2013, affecting an estimated number of over 30,000 patients in French Polynesia throughout the archipelago. Since that date until February 2014, it was described an increase number of neurological symptoms and complications including 42 cases of Guillain–Barré syndrome (GBS) that were associated with ZIKV infections [16, 17].

During the French Polynesia outbreak, two important events were described. The first one occurred in December 2013 when a patient who had initially suffered from ZIKV infection symptoms (asthenia, fever, headache and arthralgia), presented hematospermia 8 weeks later and looked for medical care. During the semen study, real-time reverse transcription polymerase chain reaction (RT-PCR) for ZIKV was performed and resulted positive (also in urine but not in blood), adding data to the evidence that sexual transmission was possible [18]. In March 2014, two cases of pregnant women were described to have a positive reverse transcription polymerase chain reaction (RT-PCR) for ZIKV in the 38 weeks' gestation and 4 days after delivery. A positive RT-PCR in their newborns was also confirmed, becoming the first vertical or perinatal transmission described [19].

Following outbreaks took place in New Caledonia (2014) with 1400 confirmed cases, Cook Island (2014) over 900 cases, Easter Island (2014), Samoa (2015) and American Samoa (2016) [16, 20, 21].

In February 2014, the first case of autochthonous transmission of ZIKV in Eastern Island (Chile), located in the south-eastern Pacific [22], was confirmed.

ZIKV infection was notified for first time in the Americas in March 2015 in Bahia, Brazil, during an outbreak of cases presenting rash, mild fever, arthralgia and conjunctivitis, whose samples showed a negative serology of Dengue and Chikungunya virus. RT-PCR of ZIKV was performed in 21 acute-phase serum specimens, from Santa Helena Hospital in Camaçari and resulted positive in seven of them (29.2%). The phylogenetic analysis confirmed the belonging to the Asian linage and a 99% identity with a sequence from a ZIKV isolate from French Polynesia [23, 24].

There has been important speculation about how ZIKV appeared in Brazil, after Pacific Ocean outbreak. Phylogenetic studies [23] associated with a review of international event, suggested that it could have happened in August 2014 during the Va'a World Sprint Championship canoe race that took place in Rio de Janerio, Brazil. Four invited countries to the event had ZIKV circulating during 2014 [25].

On 7 May 2015, for the first time, Pan American Health Organization and WHO made an epidemiological alert about the potential spread of ZIKV infection across territories where the vectors *Aedes* were present [26].

Two months later, in 17 July 2015, it was reported by Bahia State of Brazil, an increasing number of neurological disorders that included 49 confirmed GBS in patients with history of exanthematic disease (62% of them with a previous history of ZIKV and dengue infection confirmed) [27, 28].

In October 2015, the authorities of Colombia confirmed the first case of ZIKV infection. This same month, Cabo Verde confirmed the country's first outbreak of ZKV infection with 165 suspected cases reported [22, 29].

Also, in October 2015 Brazil made a communication from Pernambuco State Health Department concerning an increasing number of cases of microcephaly since August 2015. From a total yearly average number of microcephaly per 1000 live births annually reported of 62.8 (from 2010 to 2014), the number has increased up to 1248 as for 28 November 2015 [22, 29, 30]. On 13 November 2015, Ministry of Health in Brazil reported the presence of RNA ZIKV in amniotic fluid samples from two pregnant women who had presented possible ZIKV clinical symptoms at 18' weeks and 10' weeks of gestation, respectively. Microcephaly was confirmed in their two newborns [29, 31].

Until December 2015, 18 Brazil states confirmed autochthonous ZIKV transmission. According to preliminary data, 440,000–1,300,000 cases of ZIKV infections were estimated to have happened during 2015 by the Brazilian Ministry of Health [29].

From the end of December 2015 until end of January 2016, a total of 2.016, 3.836, 99 and 147 cases were reported by El Salvador, Panama and Martinique respectively. Also Venezuela reported 192 cases of ZIKV infections. During the next months ZIKV infection spread gradually by the American continent and until 1 February 2016, 25 countries from Americas, Africa and Asia had notified confirmed

autochthonous ZIKV cases. Additional seven countries (Brazil, Colombia, Cabo Verde, Bolivarian Republic of Venezuela, El Salvador, Martinique and Panama) have also reported ongoing outbreaks of ZIKV infection [22]. Dates of cases officially reported by country, until December 2016 are illustrated in Fig. 2.2 [28].

On 1 February 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC), the possible link with ZIKV infection and the microcephaly and other neurologic syndromes cases [32].

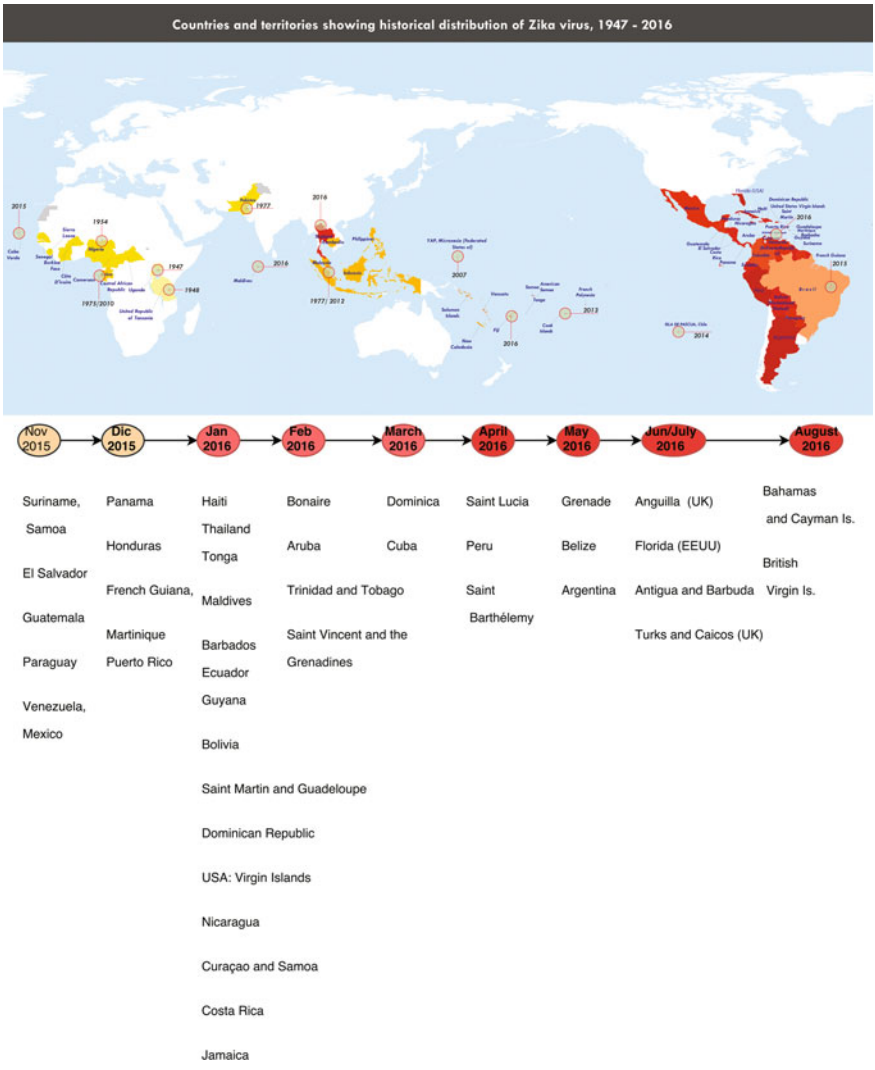

Fig. 2.2 Date of first autochthonous cases of ZIKV infection by country until August 2016 [28]

2.2 Current Outbreak

To the date of 2 September 2016, there have been four WHO meetings of the Emergency Committee under the International Health Regulations (2005) regarding microcephaly, other neurological disorders and ZIKV. Until that moment, 72 countries and territories have reported ZIKV transmission since 2007. Twenty countries have reported microcephaly and other central nervous system malformations related with ZIKV and 18 countries have reported an increased incidence of GBS. Because of the continuous viral expansion and the lack of scientific evidence, it was decided to continue considering ZIKV as a PHEIC [33, 34].

On 18 November 2016, during the fifth meeting of the Emergency Committee under the International Health Regulations (2005) regarding microcephaly, other neurological disorders and ZIKV, the PHEIC was removed because the research had already demonstrated the link between ZIKV infection and microcephaly.

Some cases have been described in Asia and Pacific, up to 20 March 2017, in India, Philippines (national), Viet Nam (national), Singapore (national), Malaysia (Petaling Jaya, Selangor), Thailand, Myanmar (Yangon) and Taiwan with only imported cases.

In Africa up to 17 January 2017, there have been described ZIKV cases in Guinea Bisau, Nigeria and Angola in which on 7 February 2017, Health officials have reported a ZIKV-related microcephaly case from Bengo province.

Finally, up to date on 7 February 2017, no additional countries or territories of the Americas have confirmed autochthonous, vector-borne transmission of ZIKV disease during the last month, but five countries have reported sexually transmitted Zika cases [35].

Up to 23 March 2017, Pan American Health Organization (PAHO) cumulative cases described a total of 20 deaths among ZIKV cases, 2807 total cases of confirmed congenital syndrome associated with ZIKV infection in America (including north, Latin American and the Caribbean and non-latin Caribbean), 551,432 suspected cases and 206,351 confirmed ZIKV infection cases [36].

In United States of America (USA), up to 29 March 2017, 5182 cases of ZIKV were reported. From them, 4886 cases happened in travellers returning from affected areas and 222 cases acquired through presumed local mosquito-borne transmission in Florida (216 patients) and Texas (6 patients). 74 cases were acquired through other routes, including sexual transmission (45 patients), congenital infection (27 patients), laboratory transmission (1 patient) and person to person through an unknown route (1 patient) [37].

Imported cases with no possibility of on going mosquito transmission have been described in Europe, from France, Spain and United Kingdom. There has been reported a total of 478 cases in Canada, up to 9 March 2017, whom 28 were pregnant women with 2 ZIKV-related abnormalities in foetuses and newborns and 3 additional sexually transmitted cases [38].

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