Zika virus outbreak in Cabo Verde Islands, West Africa: early epidemiological findings

José Lourenço[1], Maria de Lourdes Monteiro[2], Tomás Valdez[2], Júlio Monteiro Rodrigues[2], Oliver G. Pybus[1], Nuno Rodrigues Faria[1*]

Affiliations:

[1]Department of Zoology, University of Oxford, UK

[2] Ministry of Health, Praia, Cabo Verde

Correspondence to:

Nuno Rodrigues Faria (nuno.faria@zoo.ox.ac.uk)

South Parks Road, Department of Zoology, OX3 1PS Oxford, United Kingdom

Abstract

The Zika virus (ZIKV) outbreak in the island nation of Cabo Verde was of unprecedented magnitude in Africa and the first to be associated with microcephaly in the continent. Here we present its first epidemiological assessment by investigating attack and observation rates from 7,580 ZIKV notified cases and 18 microcephaly reports between July 2015 to May 2016. The basic reproductive number of the outbreak in Cabo Verde was estimated around 1.66 (95% confidence interval, CI, 1.39-1.98), similar to that reported in the Americas. Assuming that the microcephaly risk per pregnancy is identical between Cabo Verde and the Americas we extrapolate that ~56% (CI: 47 to 65)% of the population may have been infected with ZIKV. Our results highlight the need for rapid and integrated epidemiological, molecular and genomic arbovirus surveillance to tackle forthcoming outbreaks in Cabo Verde and other African nations.

Main text

Zika virus (ZIKV) was first reported in Uganda in 1947 but until recently human infections in Africa were considered rare and not associated with outbreaks or neurological complications (1). The first large ZIKV outbreak was reported in the Yap island of Micronesia in 2007 where around 73% of the population is estimated to have been infected (2). In 2013-14, a similar proportion of the population was exposed to the virus in French Polynesia, where the first ZIKV-infections associated with neurological complications were detected (3). In early May 2015, autochthonous transmission of the virus was confirmed in the northeast region of Brazil (4). Subsequent analysis of genetic data suggests that ZIKV had been circulating

undetected in the Americas at least since early 2014 (5). In February 2016, ZIKV became of Public Health Emergency of International concern, and two months later the World Health Organization and the Centre for Disease Control confirmed the association of Zika virus infection with microcephaly and neonatal neurological complications. So far, of the two known Zika virus lineages – the African genotype, restricted to the African continent, and the Asian genotype, confined to Southeast Asia and the Americas – only the later has been associated with microcephaly and neonatal neurological complications.

Recently, Cabo Verde reported 7,580 ZIKV suspected cases and 18 microcephaly cases between October 2015 to May 2016, in the first known ZIKV outbreak in Africa. Cabo Verde is an archipelago composed by 10 islands located west of the coast of Senegal, with a total population size of 532,913 in 2015. Importantly, this is also the first time that ZIKV-associated microcephaly cases are reported in Africa. While epidemiological investigations based on clinical reports in the Americas may have been obscured by the co-circulation of dengue and chikungunya viruses – which can confound case report data due to overlapping clinical symptoms with ZIKV; these were not reported to be co-circulating in Cabo Verde at the time of the ZIKV outbreak. Despite its scientific and public health importance, there is a dearth of information about the Cabo Verdean ZIKV outbreak. Here we provide the first epidemiological characterization of the ZIKV outbreak in Cabo Verde in light of the information gathered from the recent epidemics in the Americas and French Polynesia.

By the 5th of October 2015 (epidemiological week 40), the first cases of illness with skin rash were reported in the capital city of Praia, on the island of Santiago. A detailed report is available (in Portuguese) from the official Surveillance and Outbreak Response Unit of the Ministry of Health of Cabo Verde (SVIER-MS) (6). The number of ZIKV cases grew rapidly, and by the end of week 41 in 2015 there were 95 ZIKV notified infections (**Figure 1a**). The peak of the outbreak occurred in week 47 in 2015 (22-28th November). The outbreak was characterized by a single epidemic wave, and transmission ceased in week 21 of 2016 (22-28th May).

[Figure 1 around here]

Figure 1. Epidemiological characteristics of Zika virus outbreak in Cabo Verde during 2015-2016. **Panel a**. Number of ZIKV notified cases per epidemiological week in Cabo Verde (red) and in Brazil (grey tones). **Panel b** shows the risk of microcephaly along the corresponding 95% confidence intervals estimated by study (*i*) published in ref. (7), study (*ii*) in ref. (8), study (*iii*) in ref.(9) , and study (*iv*) in ref.(10). **Panel c** shows the estimated proportion of the Cabo Verdean population infected with ZIKV during the 2015-2016 outbreak, as estimated by $Pop_{infected} = m /(b \times r_{MC})$. We considered m=18 microcephaly cases across Cabo Verde as reported to the SVIER-MS, and b=10,908 births during the observation period; r_{MC}=risk of microcephaly, as shown in **panel b**. Dashed lines and transparent boxes represent,

respectively, the median and 95% confidence interval estimates of the risk of microcephaly (grey) and proportion of population infected (red).

By 29th of May 2016, 7,580 cases had been reported by health centers in four out of ten islands (Santiago, Fogo, Maio, Boavista). Two of these islands reported most cases: Santiago reported 65.1% (4937/7580) and Fogo 19.2% (1458/7580). A total of 18 microcephaly cases were confirmed, all within the four islands with reported ZIKV transmission (12 in Santiago, 4 in Fogo, 2 in Maio). Approximately 50% of all confirmed microcephaly cases were linked to reports of Zika-related symptoms in the first trimester of gestation. Sixty-four samples related to suspected Zika cases were sent to Pasteur Institute in Dakar; of these, 17 tested positive for Zika (15 were IgM positive, 2 were RT-qPCR positive); all samples tested negative for dengue, chikungunya, Yellow fever, Rift Valley fever and West Nile (11).

We first estimate the basic reproductive number (R_0) for the Cabo Verde outbreak, defined as the average number of secondary human cases generated by a single primary human case, based on weekly case counts reported by the SVIER-MS (**Figure 1 A**) (6). For this, we fit a simple exponential growth model to the weekly number of suspected ZIKV cases as previously described and implemented for Brazil regions (5). The epidemic generation time was assumed to be 10.8, as recently estimated for Feira de Santana, Brazil (7). Our model reveals an R_0 with mean 1.66 (95% CI: 1.39, 1.98) for the Cabo Verde outbreak. This is in line with the R_0 values obtained for different regions in Brazil, which varied from 1.29 to 1.98 (5). We estimate a lower bound for R_0 >1, in line with abundance and competence of the mosquito vector *Aedes aegypti* in Cabo Verde (12).

Next, we sought to quantify the attack rates of ZIKV in Cabo Verde, defined as the proportion of the entire population infected with the virus during the first epidemic wave. We calculate the unobserved AR based on the observed number of microcephaly cases (m), observed number of newborns in Cabo Verde (b), and estimated absolute risk of microcephaly per pregnancy (r_{MC}). Here, the expression for the attack rate is simply $AR=m/(b \times r_{MC})$. We considered m=18, the number of reported microcephaly cases in Cabo Verde as reported to the SVIRE-MoH of Cabo Verde, and b=10,908 live births during the same period (1 year).

We calculated the AR in Cabo Verde under four different absolute risks of microcephaly per full pregnancy (r_{MC}) from studies based in regions of Brazil and the French Polynesia (**Figure 1b**). *Study* (*i*) used a climate-driven transmission model to investigate the ZIKV-related absolute risk of microcephaly in Feira de Santana (FSA), the second largest municipality in Bahia state, Northeast Brazil; assuming an AR=65%, the absolute risk of microcephaly in FSA was estimated at 31.9 (95% CI: 28 to 36) cases per 10,000 challenged pregnancies (7). This resulted in an extrapolated AR= 51% (95% CI: 45 to 58) for Cabo Verde (**Figure 1c**). *Study* (*ii*) analysed data from 6 municipalities in 3 states of Brazil, and estimated a risk of 34.2

(95% CI: 20 to 48) microcephaly cases per 10,000 challenged pregnancies, with an assumed attack rate of 50% (9). In this case, the extrapolated AR for Cabo Verde was 48% (95% CI: 34 to 81). Using official numbers from the Brazilian Ministry of Health, *study* (*iii*) reported an absolute risk of microcephaly of 19.8 (95% CI: 10 to 29), which returns a ZIKV attack rate of 83% (95% CI: 56 to 100) for Cabo Verde. Finally, *study* (*iv*) estimated a risk of 40 (95% CI: 13 to 86) cases per 10,000 challenged pregnancies during the 2013-2014 outbreak in the French Polynesia, characterised by a 66% (95% CI: 62 to 70) attack rate (10). This resulted in an extrapolated AR=41% (95% CI: 19 to 100).

Overall, the attack rate of ZIKV in Cabo Verde was estimated at 56.1% (95% CI: 46 to 65) when considering microcephaly risk published in studies (*i*) to (*iv*). The estimated average of these attack rates (**Figure 1c**) is slightly lower than for previous outbreaks (2, 7, 10, 13), suggesting that the level of herd-immunity may still be under the threshold that would prevent additional small to medium size ZIKV outbreaks in Cabo Verde. Given the estimated AR and the number of reported infections, we estimate a low case observation rate of OR=2.53% (95% CI: 2.17 to 3.03), i.e. an estimated 25.3 cases were notified for every 1,000 infections. A low OR is not uncommon for ZIKV (7). We note that the estimated OR for Cabo Verde is not on the low end of several ORs reported in literature (7), which can be potentially explained by an absence of co-circulating arboviral infections in Cabo Verde that complicate diagnosis.

With attack rates ranging from 46% to 65%, our findings suggest that between ~249,400 to ~348,800 people may have been infected with ZIKV during the recent outbreak in Cabo Verde. Was the viral lineage that caused this large outbreak in Cape Verde introduced from the Americas or from another African country? A rapid assessment of the global air travel network (ref. (15), in http://www.vbd-air.com) suggests the presence of similar ecologies and direct air travel connections between the northeast of Brazil and Santiago island where most cases were observed. Given the timing of the epidemic (**Figure 1a**) and the high number of travellers visiting Cabo Verde from the Americas – the country received >7000 travellers from ZIKV infected countries in 2015, including direct flights from Northeast Brazil (14); it seems likely that the outbreak was caused by the Asian genotype circulating in the Americas. Moreover, recent ZIKV cases in Africa have also been reported in Angola (1 returning traveller to France and 1 autochthonous case (16)) and Guinea-Bissau (3 cases in the Bjagó islands (17)). Similar to Cabo Verde, no genetic data is available from Angola or Guinea-Bissau.

Determining the genetic characteristics of the ZIKV lineages circulating in Africa and other may have scientific and public health implications. Recent advances in portable genome sequencing allow to generate genome data in the field within days (19, 20), and can help increasing research capacity, thus reducing time to response to future outbreaks. Further, in the future, retrospective seroepidemiological surveys could further facilitate the estimation of attack, symptomatic and observation rates not only

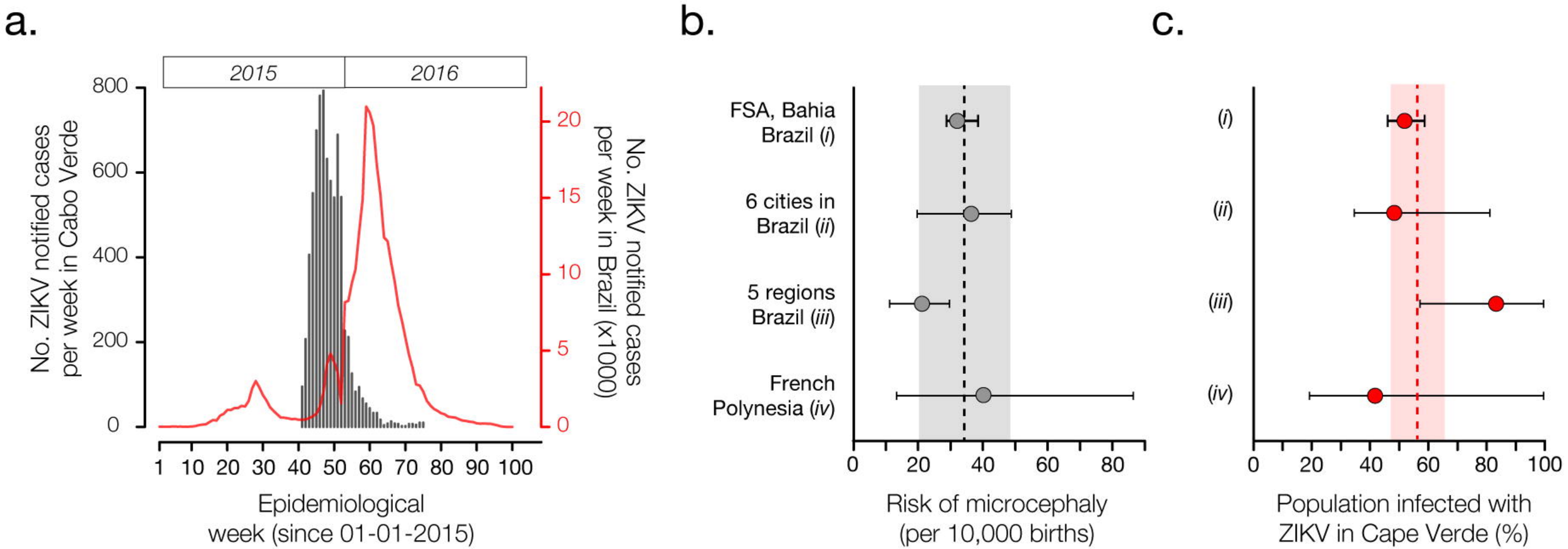
for ZIKV but also for other arthropod-borne viruses. In 2009, Cabo Verde reported >17,000 infections of dengue virus (18). Thus, Cabo Verde's epidemiological setting is unique given that dengue and Zika have caused single but sequential epidemic waves there. This offers an exceptional opportunity to evaluate the potential contribution of previous dengue virus seropositivity to the ZIKV associated risk of microcephaly.

In conclusion, our early epidemiological assessment of the largest Zika virus outbreak in Africa suggests that half of the Cabo Verde population was exposed to Zika in 2015-2016. This highlights the need improved and integrated epidemiological, molecular and genomic arbovirus surveillance system is needed to tackle forthcoming outbreaks in Cabo Verde and other African nations.

References

1. Kindhauser MK, Allen T, Frank V, Santhana RS, Dye C. Zika: the origin and spread of a mosquito-borne virus. Bulletin of the World Health Organization. 2016 Sep 01;94(9):675-86C.
2. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. The New England journal of medicine. 2009 Jun 11;360(24):2536-43.
3. Faria NR, Azevedo R, Kraemer MUG, Souza R, Cunha MS, Hill SC, et al. Zika virus in the Americas: Early epidemiological and genetic findings. Science. 2016 Apr 15;352(6283):345-9.
4. Hennessey M, Fischer M, Staples JE. Zika Virus Spreads to New Areas - Region of the Americas, May 2015-January 2016. MMWR Morbidity and mortality weekly report. 2016 Jan 29;65(3):55-8.
5. Faria NR, Quick J, Claro IM, Theze J, de Jesus JG, Giovanetti M, et al. Establishment and cryptic transmission of Zika virus in Brazil and the Americas. Nature. 2017 Jun 15;546(7658):406-10.
6. Monteiro MLS, Fortes, A. R. Boletim Informativo Semanal - Infeção por Vírus Zika (ZIKV) Ano 2016 (Semanas 1 a 21): http://www.minsaude.gov.cv/index.php/documentosite/zika-1/341-boletim-informativo-semanal-da-infecao-por-virus-zika-semana-21-ano-2016/file. Santiago, Cabo Verde; 2016.
7. Lourenco J, Maia de Lima M, Faria NR, Walker A, Kraemer MU, Villabona-Arenas CJ, et al. Epidemiological and ecological determinants of Zika virus transmission in an urban setting. eLife. 2017 Sep 09;6.
8. Jaenisch T, Rosenberger KD, Brito C, Brady O, Brasil P, Marques ET. Risk of microcephaly after Zika virus infection in Brazil, 2015 to 2016. Bulletin of the World Health Organization. 2017 Mar 01;95(3):191-8.
9. de Oliveira WK, de Franca GVA, Carmo EH, Duncan BB, de Souza Kuchenbecker R, Schmidt MI. Infection-related microcephaly after the 2015 and 2016 Zika virus outbreaks in Brazil: a surveillance-based analysis. Lancet. 2017 Aug 26;390(10097):861-70.
10. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French

Polynesia, 2013-15: a retrospective study. Lancet. 2016 May 21;387(10033):2125-32.
11. ProMED-mail. 6 November 2015. Zika virus—Suriname, Cape Verde. ProMED-mail archive no. 20151106.3770696. http://www.promedmail/ .org. ; 2015.
12. da Moura AJ, de Melo Santos MA, Oliveira CM, Guedes DR, de Carvalho-Leandro D, da Cruz Brito ML, et al. Vector competence of the Aedes aegypti population from Santiago Island, Cape Verde, to different serotypes of dengue virus. Parasites & vectors. 2015 Feb 19;8:114.
13. Aubry M, Teissier A, Huart M, Merceron S, Vanhomwegen J, Roche C, et al. Zika Virus Seroprevalence, French Polynesia, 2014-2015. Emerging infectious diseases. 2017 Apr;23(4):669-72.
14. Bogoch, II, Brady OJ, Kraemer MUG, German M, Creatore MI, Brent S, et al. Potential for Zika virus introduction and transmission in resource-limited countries in Africa and the Asia-Pacific region: a modelling study. The Lancet infectious diseases. 2016 Nov;16(11):1237-45.
15. Huang Z, Das A, Qiu Y, Tatem AJ. Web-based GIS: the vector-borne disease airline importation risk (VBD-AIR) tool. International journal of health geographics. 2012 Aug 14;11:33.
16. WHO. Zika virus, Microcephaly and Guillain-Barré syndrome, http://www.who.int/emergencies/zika-virus/situation-report/20-january-2017/en/. Switzerland, Geneva; 2017.
17. WHO. Zika virus, Microcephaly and Guillain-Barré syndrome: http://www.who.int/emergencies/zika-virus/situation-report/11-august-2016/en/. Switzerland, Geneva; 2016 11 August 2016.
18. Dengue fever, Cape Verde. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations. 2009 Nov 09;84(45):469.
19. Faria NR, Sabino EC, Nunes MR, Alcantara LC, Loman NJ, Pybus OG. Mobile real-time surveillance of Zika virus in Brazil. Genome Med. 2016 Sep 29;8(1):97.
20. Quick J, Grubaugh ND, Pullan ST, Claro IM, Smith AD, Gangavarapu K, et al. Multiplex PCR method for MinION and Illumina sequencing of Zika and other virus genomes directly from clinical samples. Nat Protoc. 2017 Jun;12(6):1261-76.


a.
2015
2016
No. ZIKV notified cases per week in Cabo Verde
No. ZIKV notified cases per week in Brazil (x1000)
800
600
400
200
0
20
15
10
5
0
1 10 20 30 40 50 60 70 80 90 100
Epidemiological week (since 01-01-2015)
b.
FSA, Bahia Brazil (i)
6 cities in Brazil (ii)
5 regions Brazil (iii)
French Polynesia (iv)
0 20 40 60 80
Risk of microcephaly (per 10,000 births)
c.
(i)
(ii)
(iii)
(iv)
0 20 40 60 80 100
Population infected with ZIKV in Cape Verde (%)