Zika virus epidemiology: from Uganda to world pandemic, an update

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Abstract

Zika virus (ZIKV) infection is an emergent worldwide public health problem. Historically, 84 countries have reported vector-borne ZIKV transmission, 61 of which report on-going transmission. It is a *Flavivirus* transmitted through arthropods belonging to the *Aedes* genus. Since 2015, ZIKV infections have increased dramatically; with 1.3 million people infected during 2015 in Brazil alone. This paper's objective is to highlight the conjectural epidemiological points of the virus' dissemination. The digital archives Pubmed, MEDLINE, EMBASE and Cochrane were searched for papers that assessed aspects of ZIKV transmission and epidemiology. The first isolation occurred in Uganda in 1947. Since then, important outbreaks were documented globally. Consequently, an emergent public health problem arose from a rapidly increasing incidence and its association with the development of neurological diseases such as microcephaly and Guillain–Barré syndrome. Key factors in the successful containment of outbreaks include surveillance of mosquitos in the neighbourhood, an early mosquito control treatment, an assertive information campaign, and the involvement of the local population and healthcare workers. As such, while ZIKV seems to be spreading globally in a similar manner to other arboviruses, such as Dengue and Chikungunya viruses, it can also be rapidly contained due to the pre-existing availability of necessary resources and regulatory tools as control measures. This review aims to provide a description of those characteristics of ZIKV infection that may be useful in the construction of effective outbreak control strategies.

Introduction

Zika virus (ZIKV) infection is an emergent public health problem around the world. According to the latest situational report of the World Health Organization (WHO), cases with evidence of vector-borne ZIKV transmission have been reported throughout history in 84 countries and territories worldwide [1]. On 1 February 2016, the WHO declared ZIKV a public health emergency of international concern, responding to multiple reports of microcephaly and neurological disorders [2]. Indeed, clinical complications following ZIKV infection are notably neurological, as the virus manifests a predilection for the central nervous system (CNS). This neurotropism is explained by previous animal experiments, which show that ZIKV breaks the protection of the blood–brain barrier, entering the CNS and causing the characteristic neurological features [3, 4].

ZIKV is a *Flavivirus* of the same family of the West Nile and Yellow Fever viruses. It is transmitted by arthropods belonging to the *Aedes* genus, especially *Ae. aegypti* and *Ae. polynesisiensis* [5]. Infection by ZIKV carrying mosquito, *Aedes aegypti*, has been associated with neurological complications such as microcephaly and Guillain–Barré syndrome (GBS) [5]. These associations were initially made by case reports of GBS in French Polynesia, describing symptoms similar to the axonal subtype in evaluated patients as a consequence of ZIKV infection [5]. Additionally, other neurological complications such as microcephaly in newborns from ZIKV infected mothers have been associated with the virus [6, 7].

The importance of surveillance is highlighted by the fact that ZIKV infections have risen dramatically since 2015, with an estimated 1.3 million people infected during a 9-month period in Brazil alone [8]. Also, the virus' neurotoxicity constitutes a major health issue due to a possible increase in microcephaly and GBS cases around the globe. Such enormous public health implications call for an urgent understanding of the origin, mode of transmission, behaviour, spreading pattern, and diagnosis of the ZIKV, which will be further studied in this review.

A great deal of epidemiological, clinical and molecular evidence regarding ZIKV has been produced and has been reviewed in a highly focused fashion elsewhere [9–14]. However, the aim of this paper is to provide public health officials and policymakers with a succinct

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overview of the evidence that may inform the development of effective control and prevention strategies.

Methods

A literature search was conducted using the digital archives Pubmed, MEDLINE, EMBASE and Cochrane. The following MeSH terms were used: 'Zika Virus Infection', 'Epidemiology', 'Public Health', 'Microcephaly', 'Social Determinants of Health' and 'Zika Virus Infection', with varied subheadings as 'clinical manifestations', 'animal models' and 'diagnosis'. All literature reviews, original papers and case reports that issued epidemiological aspects of ZIKV origin, mode of transmission, behaviour and pattern of spread were included. Additionally, epidemiological reports of WHO, CDC, ECDC and other public health organisations were assessed for this paper. The aim of this search strategy was to find literature which could describe the historical landmarks of the disease's spread, the consequences of that spread, and potential control strategies.

First isolation: Uganda

ZIKV was first isolated in April 1947 from a pyrexial sentinel rhesus monkey native to the Zika forest in Uganda, in an attempt to study yellow fever [15]. The second isolation took place in January 1948, this time from a pool of *Aedes africanus* mosquitoes obtained in the same forest [16]. Due to its being native to Zika forest, this newfound virus became known as the 'Zika virus' [15]. The first report of a human infection of ZIKV occurred in Uganda in 1964, in which a European man developed a 5-day febrile syndrome with myalgia and maculopapular rash, that was eventually confirmed by convalescent and acute serum samples that showed neutralising ZIKV antibodies [17]. Throughout the 1960s and 1970s, multiple ZIKV human isolates were obtained, confirming infections in several Asian and African countries (Egypt, Nigeria, Uganda, India, Malaysia, Indonesia, Pakistan, Thailand, North Vietnam and the Philippines) [15–18]. Non-structural gene 5 (NS5) sequencing demonstrated the existence of three lineages of ZIKV which originated infections in East Africa, West Africa and Asia [11]. Nonetheless, the first sample of human ZIKV infection outside of Africa and Asia was identified in 2007, in Yap Island in the Federated States of Micronesia, Oceania [15–18].

First outbreak: French Polynesia and association with neurological affections

The previous largest documented ZIKV outbreak took place in French Polynesia in 2013 [18]. It was during this Zika outbreak, alongside types 1 and 3 Dengue fever co-epidemics, that the first associated cases of GBS following a ZIKV infection were recorded [8]. This was reported in a case–control study in French Polynesia that took place between October 2013 and April 2014, which found a possible association between ZIKV and GBS [19]. There were two control groups: control group 1 ($n = 98$), containing patients who presented at the hospital with non-febrile illness; and control group 2 ($n = 70$), containing patients with acute ZIKV disease and no neurological symptoms. A total of 42 cases of GBS showed electrophysiological findings consistent with acute motor axonal neuropathy (AMAN) and exhibited a rapidly evolving pathology [19]. This study found an odds ratio for GBS of 34.1, with a wide but significant confidence interval (CI) (5.8, Inf). Likewise, research by Salinas

et al. and Styczynski *et al.*, found odds ratios of 4.6 (95% CI 1.1–19.0) and 6.45 (95%CI 1.88–22.10), further reinforcing the association between ZKV and GBS and confirming the early results from the Polynesian studies [20, 21].

Zika and microcephaly in French Polynesia

A retrospective study in French Polynesia found an increasing number of microcephaly cases during the 2013 and 2014 outbreaks. In 2013, four cases were reported (up from a base of three in the previous year). The following year, in 2014, this had increased to 13 cases. Out of those 13 cases, amniotic fluid tests were only possible in six patients, four of which were positive for ZIKV using PCR [22]. The estimated risk of microcephaly after ZIKV infection in the first trimester of pregnancy was 95 per 10 000 women infected. Nonetheless, the prevalence was two per 10 000 neonates [23]. The risk period for microcephaly in this study was found to be the first trimester of pregnancy, and therefore prevention measures should be strengthened during this period. Finally, although the prevalence of microcephaly in the French Polynesia was 1%, which seems low, the growing population infected with ZIKV makes this risk increasingly noteworthy [23]. Due to the potential effects of infection by ZIKV on pregnant women, physicians should consider the evaluation of cerebral abnormalities in the foetus during the second trimester of pregnancy of women living in ZIKV endemic zones [22].

The pandemic arrives to America: Brazil, Zika and nervous system affections

The latest outbreak documented occurred in Brazil close to the end of 2014, with between 0.4 and 1.3 million people estimated to have been infected during 2015 [1]. There are several theories as to how the disease arrived in the South American country. A two-step protocol DNA analysis of the virus showed its similarity with the Asian lineage, therefore suggesting its arrival during the 2014 FIFA World Cup tournament, held in June and July of that year, and also from the Va'a World Sprint Championship canoe race, held the following August [12, 24, 25]. The explanation of the disease's arrival during the football tournament seems to be imprecise, as no Zika-endemic Pacific countries were participants [26]. Even so, it is possible that spectators from Zika-endemic countries might have been present [26]. The canoe race, on the other hand, included participants from four Pacific countries in which ZIKV was circulating: French Polynesia, New Caledonia, Cook Islands and Easter Island [27]. In either case, the outbreak is generally assumed to be a consequence of such sporting events [27]. Other researchers from Canada, Brazil, UK and USA published a study suggesting the virus entered Brazil in 2013 through someone infected in that year's Zika epidemic in French Polynesia or from another Zika-endemic country [28]. This theory is also supported by the increase in air travel from Zika-endemic areas to Brazil by almost 50% during 2013 and by mathematical modelling of the outbreak [28, 29]. The growing number of infected people by local transmission made it necessary for Brazil to report ZIKV as a noteworthy disease in 2016 [2]. Additionally, GBS was temporally and geographically associated with the presence of ZIKV in Brazil, Colombia, El Salvador, Martinique, Panama, Puerto Rico, Suriname and Venezuela [30, 31]. In contrast to the AMAN subtype found in patients in French Polynesia, case reports in Latin America suggest AIDP as the predominant subtype in this region [32].

Zika and microcephaly in Brazil

The first association with microcephaly in Brazil occurred during September 2015, as the number of newborns with the disease increased in correlation with ZIKV-infected pregnant women. The prevalence of microcephaly in involved outbreak states was 2.8 infants per 10 000 live births, with more than 4000 suspected cases reported in February 2016. Between November 2015 and July 2016, some 8301 cases of microcephaly were documented in Brazil [22, 32]. Reports also showed a rapidly increasing spread over South and Central America from October 2015 onward [33].

In the Americas, 20 countries have confirmed a total of 2311 cases of ZIKV infection and association with congenital syndromes [27]. A study in Brazil identified 343 pregnant women who were expecting delivery by the 31 July 2016, of whom 134 were positive for ZIKV. The results showed nine foetal deaths: five miscarriages in the first trimester, two miscarriages in the second trimester, and two stillbirths in the third trimester. Adverse outcomes after ZIKV infection occurred regardless of the timing of the pregnancy. From the ones that tested positive for ZIKV, 46.4% had adverse outcomes. In contrast, 11.5% of the cohort that tested negative for ZIKV developed adverse outcomes. The outcomes constituted 9% for restriction in growth and 4% for microcephaly. These results demonstrate that ZIKV infection during pregnancy is a severe risk for the development of microcephaly in foetuses [8].

The presence of clusters of microcephaly alongside other neurological disorders related to ZIKV was sufficient for the declaration of a Public Health Emergency of International Concern (PHEIC) by the WHO on the 1 February 2016 [2]. High incidences of microcephaly and GBS have been observed in populations in which Zika outbreaks have occurred. In turn, laboratory evidence from both *in vitro* and animal models support the plausibility of a link between these conditions and ZIKV infection. However, the specific pathophysiological mechanism remains unclear [4, 33–35].

Zika and other clinical manifestations around the world

Approximately 80% of patients infected with ZIKV are asymptomatic [14]. Hospitalisations are uncommon, and death is rare [36]. However, these features are not pathognomonic for the disease as they may also be present in other *Flaviviridae* infections and therefore cannot be relied upon in isolation for diagnosis [37].

The incubation period is between 2 and 14 days [38], with clinical manifestations consisting of: low fever (<38.5 °C), headache, retro-orbital pain, bilateral non-purulent conjunctivitis, maculopapular rash, arthralgia with oedema on extremities, anorexia and occasionally abdominal symptoms such as diarrhoea and pain [39, 40]. Symptoms that may aid a clinical practitioner in differential diagnosis are conjunctivitis and limb oedema, which manifest more commonly after ZIKV infection in comparison to Dengue virus (DENV) and Chikungunya infection. Hepatomegaly, leukopenia and thrombocytopenia are also less common in ZIKV than in DENV [39].

In 2016, sensorineural hearing loss was reported in a case of congenital ZIKV, implicating a possible complication other than microcephaly in newborns [41]. Additionally, a prospective case study in Colombia and Venezuela including 43 patients found that babies born with ZIKV infection presented optic disc abnormalities, optical nerve hypoplasia, glaucoma, pigment mottling and chorioretinal atrophy with a predilection for the macula [42]. Intrauterine and neonatal death may also occur [9]. In fact, Chauchemez et al. reported, in a retrospective study, eight cases of microcephaly, five of which were aborted and three were born [31].

The clinical spectrum of ZIKV infection remains a matter of investigation. Other manifestations have been reported such as: ocular flutter, meningoencephalitis, haematospermia, hearing difficulties, subcutaneous bleeding and acute myelitis [31, 43–45].

Diagnosis

Diagnosis of ZIKV infection is based on three pillars: first, the evaluation of clinical symptoms; second, the finding of an epidemiological association between infection and endemic zones; and third, confirmation by serological and molecular laboratory findings [46]. However, each of the pillars alone does not suffice to diagnose ZIKV infection, as the virus is very similar in structure, clinical features and geographical location to another flavivirus, especially Dengue, and togavirus like Chikungunya [37, 47]. The gold standard for diagnosis is a real-time PCR (RT–PCR) on body fluids chosen depending on each patient's characteristics [9, 48]. ZIKV can be found in semen, saliva, blood, cerebrospinal fluid, amniotic fluid and urine. Serum samples should be taken no more than 10 days after symptom onset, as identification of the ZIKV RNA becomes more difficult. Nevertheless, ZIKV infection during pregnancy is associated with prolonged viraemia and the virus has been detected in the serum of pregnant women up to 53 days post-exposure [49]. Saliva samples may also be taken within this range of time with an increased rate of molecular detection of the virus. However, it is especially used in patients with whom serum samples are difficult to take, such as the paediatric population [9]. On the other hand, new investigations regarding urine samples of infected individuals have shown positivity for ZIKV RNA after ten days of symptom onset. This discovery brings an essential tool for diagnosis in cases in which obtaining samples is not possible within ten days of symptom onset [50]. Finally, diagnosis of ZIKV infection in newborns or aborted foetuses can be achieved by confirming viral RNA (vRNA) in their brain or serum and mother's placenta [31], with a positive RT–PCR result being conclusive for ZIKV diagnosis. If results are negative, serum antibodies and IgM ELISA should be collected to confirm or discard the diagnosis [47]. Importance of early diagnosis lies in ZIKV's sexual transmission, foetal health problems and neurological complications that can be prevented [9].

Transmission

The rapid spread of the pathogen occurs due to diverse transmission pathways; however, the primary mode of transmission is mosquito-borne [51]. A sylvatic transmission cycle involves non-human primates and forest species of *Aedes* mosquitoes. In urban and suburban environments, ZIKV is transmitted in a cycle of human–mosquito–human bites by two species of the *Aedes* subgenus: *Ae. aegypti* and *Ae. albopictus*. The vectors usually bite humans during daytime, and can be found both inside and outside houses. *Ae. aegypti* mosquitoes are spread extensively in the Americas (excluding Chile), where the climatic conditions are appropriate for vector breeding. This is partially responsible for the ZIKV epidemic reported since 2015. *Ae. albopictus* is distributed in regions with cooler temperatures, such as New York and Chicago in northern USA and in parts of southern Europe

[31]. The *Aedes* mosquito species are found widely around the world, and in consequence, the likelihood of the outbreak to spread to new countries remains high [6, 52]. Furthermore, climate change must be accounted for, as it expands vectorial capacity [53]. Species distribution modelling techniques have predicted that, due to the broadly tropical and sub-tropical regions worldwide with suitable environmental conditions, which also have a larger susceptible human population, there is a high risk of introducing and establishing new autochthonous transmission [31]. Some studies also assess the possible competence of *Culex* species as a vector. However, due to conflicting results, additional evidence is needed to confirm these preliminary findings [54].

Substantial evidence also exists of non-vector transmission. Transplacental transmission during pregnancy (from mother to foetus) has been identified by detection of ZIKV RNA in the amniotic fluid of mothers whose children show cerebral abnormalities in ultrasonography, as well as the identification of the virus in brain tissues and placentas of children born with microcephaly. Peripartum transmission was documented in two infants: in one case the child exhibited symptoms, while the other was asymptomatic [55]. ZIKV RNA load has also been identified in breast milk, with much higher loads as compared with serum, which represents a risk of viral transmission while breastfeeding [56]. Between the 16 October 2016 and 9 March 2017, 13 countries reported sexual transmission of the ZIKV [57]. These reports comprise probable transmission from male to female, and male to male, through vaginal, anal and oral sexual intercourse [58]. The virus can be passed from an infected person before their symptoms start, while they are symptomatic and after their symptoms end [51]. So far, the maximum documented virus time of survival in semen of symptomatic men is 125 days [59]. Further evidence is needed, but the virus may also be passed by someone infected, who never develops symptoms [60]. Multiple reports of blood transfusion transmission cases in Brazil have been published [61–63]. In spite of testing positive for vRNA, four probable cases of transfusion transmission did not develop symptoms compatible with the virus [61, 62]. Previous to the current outbreak, four documented cases of infection were known to have occurred through laboratory exposure [51]. Direct transmission can happen through the skin or mucous membranes, although it is uncommon [26]. Finally, one case of an Australian man bitten by a monkey in Indonesia, and who subsequently developed ZIKV 5 days after the incident, led to speculation of this as a potential route of transmission [64]. However, it is still undetermined due to the possibility of his also being bitten by a mosquito during his stay [64].

Between January 2015 and 9 March 2017, 70 countries and territories have reported evidence of mosquito-borne transmission of the virus according to the ECDC; 13 countries have reported evidence of person-to-person transmission of the virus, via a sexual route [57]. Moreover, 31 countries have reported microcephaly and other CNS malformations in newborns potentially associated with ZIKV infection [57]. Four additional countries – Saint Martin, Bolivia, Trinidad and Tobago and Curaçao – have reported GBS associated with ZIKV infection [57].

Insights from mathematical models

Mathematical models of ZIKV transmission dynamics reaffirm the importance of a variety of public health strategies. Massad *et al.* devised a model which combined data from the transmission dynamics of ZIKV in French Polynesia with travel data [29]. This

mathematical model predicted an expected incidence which closely matched that of the observed weekly cases and added to the growing body of evidence suggesting French Polynesia as the source of the infection. With regards to the timing of the infection, the model predicted a date of introduction of the disease that preceded the sporting events of 2014. The need for constant epidemiological vigilance is highlighted by this finding since the disease was most likely introduced before the large international gatherings that took place.

Other models suggest that public health interventions must be both effective and enduring in order to control the spread of the disease. The agent-based model proposed by Moghadas *et al.* considered the transmissibility of asymptomatic infection, producing lower estimates of the contribution of sexual transmission than previous deterministic models [60]. This agrees with the model proposed by Maxian *et al.*, in which sexual transmission was considered to be of little importance in high-transmission scenarios [65]. However, control of sexual transmission is not unimportant, since the model by Moghadas *et al.* also predicts second waves of infection if the asymptomatic transmission is not addressed [60].

The direct impact of vector control strategies has also been studied. Analysis of a local outbreak in the Miami-Dade County by Marini *et al.* suggested that a reduction in mosquito abundance of 50% before the introduction of the virus could have prevented 51.5% of the cases [66]. Wang *et al.* predicted that the continued release of male and female Wolbachia-containing mosquitos could have had a dramatic effect on the spread of the disease in Brazil [67]. Of note, this measure was only effective if implemented in the long-term, with little impact if implemented only at the onset.

ZIKV in animal models

As the Zika epidemic progresses, the study of its pathogenesis has gained great interest in the medical community. Development of numerous animal-based models to understand its pathophysiology, its action in pregnancy and foetal development, as well as the possibility of developing a vaccine and a treatment, are on the cutting-edge of science. The most often used models for these investigations have been the murine models (both immunocompetent and immunosuppressed), guinea-pigs and non-human primates [68].

Recent murine models have shown potential for determining neurovirulence of different ZIKV strains. A recent study on immunocompetent CD1/ICR murine models showed an 80–100% age-independent mortality rate after intracranial inoculation of MR766 – a 1947 Ugandan ZIKV prototype strain [69]. It is important to underline that the route of inoculation was definitive for the initiation of disease. While the intra-peritoneal inoculation route did not show any symptoms of the disease, the intracranial route showed affection of the CNS confirmed by histopathology. Widespread variations have been observed, with inflammatory changes in the cerebral cortex showing mixed leptomeningeal and parenchymal inflammation with extensive glial proliferation and neuronal cell death [31, 69]. Other studies have shown neuronal degeneration, softening, infiltration of round cells, infiltration of Crowdy Type A bodies and encephalitis in post-mortem histopathological studies of murine brains infected with the virus [70]. Regarding other clinical manifestations, no mice showed any retinal changes [69]. Similarly, a study showing intracranial inoculation of 35-day-old immunocompetent

mice with this same prototype demonstrated signs of disease during a 5–15-day time-lapse after inoculation [65].

Guinea-pigs have also been used to understand the course of other transplacental viral infections. ZIKV studies on guinea-pigs have shown low viraemia on non-pregnant animals [68]. No viraemia was detected on pregnant guinea-pigs or their pup's blood, plasma or tissues, or other weight manifestations. However, antibodies were found in pups and their mothers, thereby posing immunocompetent guinea-pigs as an ideal model for the ZIKV-associated immune response but not ideal for the pathogenesis of complications of ZIKV infection [68].

Experiments in macaques have shown that neutralising antibodies are produced in response to the injection of ZIKV RNA into plasma [71]. This protects the organism from further infection and permits the development of specific T-cell response against the virus. Short-term viraemia follows infection in non-pregnant macaques, which usually resolves 10 days post-infection. However, infections in pregnant macaques show a more prolonged viraemia. ZIKV has been identified in macaque blood up to 57 days post-infection [71]. Finally, an important finding on rhesus monkey models was that despite blood clearance of vRNA, the virus was still detected in saliva, urine and in cerebrospinal fluid, indicating the presence of ZIKV in some tissues at low levels [72]. The vRNA was also found in the brain, eye and placenta of foetal tissues of macaques during pregnancy [73].

Social determinants of disease

All illnesses are immersed in a context that determines in an extensive manner the characteristics of the disease's course. The transmission of the ZIKV, for example, partly depends on conditions which perpetuate the vector cycle. This includes standing water reservoirs where eggs laid by the mosquito can find an optimal environment to develop, such as buckets, rainwater gathered in puddles, pools, drums, flower pots, empty cans, etc. [6, 52]. Rapid urbanisation in conditions of extreme poverty contributes to deforestation, exposing populations to different vectors and pathogens with greater frequency. Furthermore, despite widespread exposure to the vector in endemic areas, evidence has shown that poverty and inequality are factors that make people more vulnerable to develop ZIKV-related microcephaly (as shown in the economically deprived northeast region of Brazil) [74]. This social determinant of disease relates to the lack of basic services, in particular the persistent absence of water services, as well as problems with the establishment of sewage, residue collection and the use and disposal of non-biodegradable material [75]. Finally, phenomena such as population growth, migration, uncontrolled urbanisation and poverty belts in cities facilitate vector breeding and the perpetuation of the disease cycle [74, 75].

Lessons learned

On 18 November 2016, the Director-General of the International Health Regulations (IHR) accepted the recommendations of the Emergency Committee and declared the end of the Public Health Emergency of International Concern (PHEIC) [76]. However, ZIKV infection and its complications are still a concern for public health. Despite a decline in cases of ZIKV infection registered in many territories, the virus continues to spread geographically to areas where vectors are found [1]. Therefore, in order to prevent the establishment of new transmission

chains, it is necessary to undertake several strategic public health interventions:

- Intensify vector-control measures and the strategic intervention in public health risk communication, community engagement activities, personal protection against mosquitoes and appropriate advice for the caregivers of those affected [1].
- Surveillance needs to be assured through an optimal preparedness plan by local, national, and international authorities, as well as mosquito control professionals and national laboratories. A documented example of the success of such plans occurred in the Chikungunya outbreak in Montpellier, France 2014 [77]. The outbreak was rapidly contained thanks to a prompt attribution of responsibilities, an aggressive communication campaign, and continued vector control interventions. This included the use of general measures to avoid mosquito bites, as well as the use of disinfectants to which the virus is vulnerable such as 1% sodium hypochlorite, 70% ethanol or 6% hydrogen peroxide, among others [77, 78].
- The screening of TORCH, dengue and other arboviruses during pregnancy, taking into account that the synergic potential is given by the presence of immunity and/or seropositivity of another virus can cause atypical presentations of the disease or absence of the symptoms, as well as an extension of the spectrum of the maternal–foetal presentation [79].
- Enable the 'massification' of education, in particular regarding the epidemiology of the disease and the general measures that must be taken to prevent transmission by the public health authorities of each country [40]. Regarding travellers, it is important to take into account the differential diagnosis of other travel-related illnesses, the use of measures to avoid mosquito bites and the fact that travellers who plan to become pregnant soon should refrain from travelling to areas where the transmission of the ZIKV may be active.

Conclusion

ZIKV outbreaks produce devastating and lasting effects in the regions in which they occur [80]. Despite the danger having seemingly abated, for now, authorities should not be apathetic. The geographical spread of the virus and the severity of its diverse health complications, coupled with increasing cross-border travel and climate change increase the habitable environments for vectors. Therefore, it is imperative that the international public health community and national policymakers make use of this window of opportunity to put in place appropriate measures before another – possibly worse – outbreak occurs. They can do so by taking advantage of pre-existing regulatory and public health infrastructure [12]. Early vector control, an assertive information campaign, and the involvement of the local population and healthcare workers are key factors in the successful containment of outbreaks.

Consideration of the social determinants of health suggests that urban planners play a key role in the prevention of outbreaks and in the amelioration of the disease's spread. There is evidence of how integrated prevention can improve the public health response to arbovirus outbreaks and successfully contain the spread. Responsible urbanisation schemes including adequate water and waste management and sustainable urban development that avoids encroaching on vector habitats are key strategies that fall outside of the scope of health authorities. This highlights the need for an interdisciplinary approach to the control and prevention of the ZIKV spread.

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