***Review Article***

# Zika Virus in Africa: Epidemiology and Determinants

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## ABSTRACT

Zika virus (ZIKV) that was less known for decades suddenly became a global health emergency at the beginning of 2016. The virus was first discovered in the Zika forest of Uganda in 1947, and the first confirmed human infection was reported in Uganda between1962-1963. From its origin in East Africa, ZIKV then spread to West and Central Africa with a limited occurrence in North Africa. ZIKV has been circulating in Africa for over 60 years, but less attention had been given, not until its recent outbreaks outside Africa and its discovered association with adverse congenital disabilities.

Climate, sociodemographic factors, and increasing human density impact the spread of ZIKV in Africa, as in other areas. Furthermore, ZIKV transmission is also affected by several unique factors, including the potential risk of sexual transmission, as well as large numbers of refugees and other travellers from ZIKA endemic areas across Africa, and all over the world. ZIKV is known to cause several debilitating neurological complications, including microcephaly in newborns and Guillain-Barré Syndrome (GBS) in adults.

This review thus aims to highlight the epidemiological evidence and distribution of ZIKV in Africa with a focus on determinants, complications as well as management. We identified a need to improve surveillance mechanisms as a critical step to enable prompt detection and avert potential outbreaks of the disease in the continent.



*Keywords: Zika Virus, Epidemiology of Zika, Africa, Determinants, microcephaly.*


*(*Structure the abstract: Introduction; Aim; Methodology; Results/Discussion and Conclusion*)*

## 1. INTRODUCTION

ZIKV is an arthropod-borne virus (arbovirus) of the family Flaviviridae and genus Flavivirus, and it is spread by a female Aedes mosquito that is a daytime-active [1]. This same family of Flavivirus genus can also cause yellow fever, dengue, Japanese encephalitis, West Nile virus disease [2]. This novel teratogenic infectious agent was first found in a sentinel rhesus macaques monkey showing symptoms of febrile illness in the Zika forest near Entebbe, Uganda, in 1947. The virus was then isolated in Aedes mosquitos in 1948 [3,4]. ZIKV is transmitted generally through mosquitoes but with other non-vector borne modes like sexual transmission, blood transfusion, or other fluid transmissions [5,6]. ZIKV is typically asymptomatic [3] and causes mild infection in humans but is associated with severe neurologic complications like Guillain-Barré syndrome, meningoencephalitis [7] and adverse fetal outcomes such as microcephaly, blindness, placental insufficiency, and fetal demise or even death of newborns [8]. To date, significant laboratory-based evidence suggests that African strains of ZIKV can cause higher rates of infection, viral reproduction, cell death, and antiviral responses [9].

Subsequent epidemiological studies show that ZIKV has a broad geographical distribution in Sub-Saharan Africa and south-east Asia [4]. ZIKV has been continuously circulating across Africa for decades, with at least 25 African countries having widespread human exposure [9]. The first human infection was identified in 1954 in a 10-year-old female Nigerian,

although it was misunderstood for Spondweni [10]. However, the first confirmed human infection was reported in Uganda between 1962-1963[4]. Even though it was known to infect humans, not much research was done about the ZIKV and was often misdiagnosed for other Aedes borne infections (Dengue, Yellow fever, Chikungunya) due to similar clinical manifestation and serological cross-reactivity with closely related viruses [3].

The spread of the virus was silent for 60 years, with less than 20 reported cases in Africa and Asia until its re-emergence in 2007 with the Yap Island and Gabon outbreaks [11]. Ever since this re-emergence, over 800,000 cases had been reported outside Africa; however, this number of cases is believed to be highly underestimated due to the asymptomatic nature of ZIKV infection [12]. (Cases are cases, and asymptomatic infections are asymptomatic infections – they are two different entities) ZIKV suddenly became a global health emergency at the beginning of 2016 due to its association with GBS, microcephaly, and other congenital disorders [3, 4, 7]. In 2016, over 7,490 suspected ZIKV disease cases were reported in Cabo Verde [13]. The focus was directed more on the western countries, until neglected Africa came in light after Zika related microcephaly cases were suspected[14] in West Africa, 6 cases from Guinea-Bissau in 2016[9], and 72 cases from Angola in 2017 and 2018 respectively and other regions of Africa[15] By 2019, over 87 countries had reported evidence of ZIKV. In Africa, information about ZIKV circulation and specific cases remains limited; this review thus aims to highlight the epidemiological evidence and current situation of ZIKV in Africa with a focus on epidemiology, determinants, complications as well as management.

(Even a Narrative Review such as this must outline the Methodology. What were the search-engines used in retrieving the Literature discussed? What types of Literature? How were these selected/discarded?)

## 2. MOLECULAR EPIDEMIOLOGY

There are two major lineages of ZIKV according to Phylogenetic analysis, known as the Asian and African lineages [16]. Previous research has shown that ZIKV has circulated in Africa for decades, but no case reports or human studies have yet investigated in-depth the effects of the African lineage on pregnancy and birth outcomes. Studies of the African lineage in-vitro and in animal models suggest an increased severity in pregnancy compared with the Asian lineage, causing foetal loss rather than birth defects [17]. The differences in the pathogenicity and epidemic potential of these viral lineages and strains are not yet fully understood [9]. Fayo O et al. reported two independent recombinant strains of ZIKV that were introduced into West Africa from East Africa. The first viral introduction into Côte d'Ivoire in 1995 and Senegal around 1985 was related to the strain which possibly moved from Uganda around 1940. The second introduction was associated with a Nigerian strain when ZIKV probably moved from Uganda to Nigeria and the Central African Republic around 1935. From Nigeria, the virus spread to and circulated within Senegal between 1950 and 1965. After which it spread to Burkina Faso around 1980 and back to Senegal around 1985. Moreover, an additional ZIKV lineage from Uganda probably spread to Malaysia around 1945, and from there, the virus reached Micronesia around 1960, forming the Asian strain [18].

## 3. EPIDEMIOLOGICAL DISTRIBUTION OF ZIKV IN AFRICA

ZIKV was identified in Uganda in the Zika forest in 1947 during Yellow fever surveillance; Zika Virus was later discovered in humans in 1952[3]. Numerous serological studies since the discovery of ZIKV have enabled the mapping out of the geographic distribution of human infections with the virus, spanning the tropical regions in Africa to Asia [18]. With a total of 87 countries and territories showing evidence of autochthonous mosquito-borne transmission of Zika virus (ZIKV) as of July 2019, and affecting four of the six WHO Regions (Africa, Americas, South-East Asia, and Western Pacific Region) [19].

**Table 1: Summary of African Countries by region with reported evidence of ZIKV**

| Region/Country | Year |
|---|---|
| **East Africa** | |
| **Uganda** | 1948 (Isolated in mosquito) [3]<br>1952 (First human case) [20]<br>1967,1969,1984 (Neutralizing antibodies detected) [21,22] |
| **Tanzania** | 1945,1947-1948 [23] |
| **Ethiopia** | 1960-1964 [24]<br>2018 [25] |
| **Kenya** | 1964,1966 (Antibodies detected) [26] |

| | |
|---|---|
| **Somalia** | 1966 [21] |
| **Djibouti** | 1991-1992 [27] |
| **Zambia** | 2013 (Zika IgM antibodies detected) [28] |
| **Other East African Countries** | Mozambique in 1957 [29], Burundi [30], Djibouti in 1991-1992 [27], Sudan [31], Seychelles [32] and Madagascar in 1977 and 1986 [33]. |
| **West Africa** | |
| **Nigeria** | 1950s-1980s (Zika antibodies in human samples) [34,35] |
| **Angola** | 1960 (ZIKV detected in human sera in different localities)[36]<br>1971, 1972 (ZIKV was again detected)[37]<br>2016 (2 cases confirmed in Luanda and Bengo)[38] |
| **Central African Republic** | 1961, 1962 (High sero-prevalences documented) [39,40] |
| **Senegal** | 1962-1990 (Initial detection of virus) [41,42]<br>2000,2008,2013 ( Recent cases reported) [43] |
| **Ivory Coast** | 1963-1965 (suspected ZIKV in circulation) [39,40,44]<br>1997-1998 (ZIKV antibodies detected in Abidjan) [45] |
| **Guinea Bissau** | 1964-1965 (positive human sera samples reported) [39,46]<br>2016 (4 cases confirmed) [47] |
| **Gabon** | 1967,1975,1979-1980 (Libreville exposed to ZIKV) [39,48]<br>2007 (ZIKV circulation detected ) [11] |
| **Cameroon** | 1984, 2010 (ZIKV was detected) [49,50]<br>2015 (ZIKV detected in blood donors sample) [51] |
| **Cabo Verde** | 2016 (The most extensive urban outbreak with over 7000 human cases notified and 18 ZIKV-associated microcephaly) [19, 52] |
| **Others West African countries** | ZIKV circulation was suspected in Burkina Faso [18], Mali, Benin, Chad, Togo, Niger [39], Republic of Congo [53], Liberia [39,54] and Sierra Leone [55] |
| **North Africa*** | |
| **Egypt** | 1950s (ZIKV detected in human samples) [56] |
| **Morocco** | 1968-1969 (ZIKV detected in human and birds) [39] |

** North Africa has seen lesser of the Zika disease cases compared to other African regions probably due to the unfavourable conditions for mosquito breeding.*

## 4. PATHOGENESIS

ZIKV belongs to; Group: IV ((+) ssRNA), Family: Flaviviridae, Genus: Flavivirus, Species: Zika virus [57]. It is an icosahedral, enveloped, non-segmented, positive-sense, single-stranded RNA virus which has a diameter of 40nm, with an outer coating and dense inner core [58]. ZIKV RNA comprises 10,794 nucleotides coding 3,419 amino acids, which are similar to the Spondweni virus. [4, 59]. This virus can quickly be adopted from arthropods to vertebrates. Cellular receptors are transmitted by E (envelope) glycoprotein, and this is followed by endocytotic uptake and uncoating of the nucleocapsid, which helps to release viral RNA into the cytoplasm. There is a production of modified viral polyprotein followed by the collection of the immature virions in secretory vesicles and endoplasmic reticulum before being released [58, 59]. Zika virus antigens are found entirely in the nuclei of infected cells, suggesting a location for replication that makes it different from other flaviviruses. The virus starts with an infection of dendritic cells near the site of inoculation and spreads to lymph nodes and the bloodstream. The incubation period is about 10days in mosquitoes while 4 to 5 days in the human host [60].

(Discuss mild forms, severe forms, mother-to-fetus transmission, congenital Zika-virus fever, pathogenesis of complications and mortality in greater detail. What is the Disease Burden due to Zika virus fever?)

## 5. TRANSMISSION

### 5.1 Vector-borne transmission

ZIKV is a mosquito-borne Flavivirus and is usually transmitted by Aedes mosquitoes [1]. This is the primary mode of transmission in the tropical and subtropical areas of Africa and other regions around the world that are infested with Aedes aegypti, Aedes albopictus, and other variety of Aedes mosquitoes [61]. When the mosquito bites an infected person with ZIKV, the virus enters into the mosquito, and when it bites uninfected person, the virus enters into the bloodstream and causes infection [57]. (Need to discuss vector-borne transmission in greater detail)

### 5.2 Non-vector borne transmissions

Sexual transmission: substantial evidence confirms that ZIKV can be transmitted through unprotected sex with an infected person. Laboratory evaluation of the cases reported in 2008 and 2013, stated that ZIKV was detected in semen [62]. Zika virus sexual transmission has been reported through sexual contact between people coming from endemic areas and those in the non-endemic areas [63]. The virus is also transmitted in both symptomatic and asymptomatic infections and through oral, anal, and genital intercourse between male and female, or similar sex [4, 57].

Blood transmission: ZIKV is a new challenge for blood transfusion, especially during ZIKV outbreaks. In 2016 a case of transfusion-transmitted infection was detected in Brazil. ZIKV RNA was detected in most of the blood donors from Florida and Texas in 2017 [4, 57].

Other body fluid transmissions: current evidence shows that ZIKV RNA has been isolated in blood, amniotic fluid, semen, urine, saliva, breast milk [64,5], and cerebrospinal fluid, indicating the significant potential of fluid transmission [5,65,2]. ZIKV in saliva has been documented to be twice as much as that in blood, implying the enormous possibility of ZIKV transmission. Saliva transmission plays a role in sporadic outbreaks in non-endemic areas [66]. ZIKV can be transmitted through tears and sweat, because eyes are the site of virus replication, increased tear secretion during conjunctivitis or uveitis can be a mode of shedding of the virus [5, 6]. The virus is also present in urine samples of ZIKV patients even after the onset of symptoms. Current evidence suggests that kidney tissue is a suitable environment for the replication of the virus [66, 67].

Maternal-fetal transmission: Pregnant mothers suffering from ZIKV have higher chances to spread the infection to the fetus. The virus enters through the placenta and damages the growing brain of the fetus, especially for mothers infected during their first trimester [4]. The intrauterine transmission was confirmed during the Brazil outbreak [68], and also perinatal transmission was reported in France in 2013 [4, 57]. Viral RNA was spotted in the amniotic fluid of pregnant mothers, although not all pregnant women infected with ZIKV may transmit the infection to the fetus [68]. In some clinical cases, ZIKV was detected in breastfeeding children, although ZIKV transmission from breast milk is suggested, breastfeeding is still considered safe for all newborns [66].

## 6. DETERMINANTS

~~Basing~~ Based on the current understanding, most people without previous exposure to ZIKV are susceptible to infection [69]. Inhabitants of areas with ongoing transmission of ZIKV from mosquitos to humans are at an increased risk of infection, as well as individuals with sexual partners who are infected [5, 6, 70]. Recent studies link sexual transmission, particularly to people or travellers from endemic areas returning to areas without mosquito transmission [70, 71, 72]. Homes with open or unscreened doors and windows, especially in areas with ongoing mosquito transmission, increase the risk of ZIKV infection [73]. (Transmission of flavi-viruses by mosquitoes is a complex issue, and frequently controversial in parts. Discuss vector-breeding, transmission by vectors and control in greater detail). Pre-existing herd immunity is also a key determinant for the future population at risk, especially among the newborns as the immunity determines the risk of ZIKV infection in women of childbearing age [74, 75].

Human social factors may determine ZIKV infection, for example, human density and poverty, among others, are related to higher rates of transmission of *Aedes*-borne pathogens amongst humans [76]. More impoverished African rural areas have lower quality housing, without window screens (The vector also breeds within houses and buildings. How effective is such screening?) and often more aquatic breeding habitat (Detail required. The aquatic breeding habits of Aedes is vastly different from the remaining mosquitoes) plus poor drainage (again) [77], leading to higher mosquito abundance and biting rates [78]. Besides, population movements among African countries, primarily as refugees, determine the rate of spread of infection into pathogen-free areas [73, 74]. Environmental factors such as temperature and humidity favour breeding of mosquitoes and thus play a critical role in sustaining the mosquito population carrying the ZIKV [76, 77]. Given the warm tropical climate in most parts of Africa, Aedes mosquitoes easily thrive, presenting a significant risk of transmitting not only ZIKV but also other mosquito-borne infections.

## 7. DIAGNOSIS

Clinically, Patients with ZIKV infection often are asymptomatic in initial stages, with about 20% [79] showing clinical symptoms after 3 to 10 days of infection [80]. Patients usually present with fever, maculopapular rash, arthralgia, myalgia, conjunctivitis, headache, retro-orbital pain, and emesis, as seen in Cabo Verde [52], but these can often be misunderstood for Chikungunya virus (CHIKV) or dengue virus (DENV) [3,4]. Usually, the fever subsides in 3-7 days, while arthralgia can persist for a month [81].

## 7.1 Laboratory diagnosis

For laboratory confirmation of ZIKV, various specimens can be used, such as; serum, saliva, tissues, urine, and whole blood [79], while in pregnant women, amniotic fluid can be used for diagnosis [4, 82]. Some investigations found the detection of ZIKV RNA within a week in Saliva and thus recommend both blood and Saliva for better sensitivity in acute stages and use urine for later stages of the disease [6]. Using the ~~mentioned~~ said specimens, ZIKV can then be confirmed through laboratory investigations of ZIKV RNA or antigen or IgM antibody [6, 81, 83]. To detect ZIKV-RNA, viral proteins (NSI) and live virus, RT-PCR, IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA), and virus isolation can be used respectively [79, 84]. These methods are used for both mosquito surveillance and the diagnosis of the patient.

~~RT-PCR test; in~~ In countries with advanced laboratory capacities, a ZIKV RT-PCR assay should be the first-line test due to its sensitivity even in the early stages of infection [83, 84]. Since the timing of infection is hard to establish, a negative RT-PCR does not exclude infection [79]. However, it is the most accurate and rapid test used worldwide

~~IgM-ELISA Test;~~ In endemic countries, due to lack of laboratory facilities, IgM ELISA or rapid tests using blood samples are used for recent exposure. [4,83]. When laboratories are using rapid tests, combined NS1 antigen and IgM antibodies should be considered to rule out cross-reaction with “dengue-like disease.” With this test, IgM antibodies are detected as early as 4–5 days and up to 12 weeks or more after the start of symptoms [84]. (IgG?)

~~PRNT test; all~~ All positive or questionable IgM ELISA results should be confirmed by a plaque reduction neutralisation test (PRNT). However, this technique is limited to a few laboratories; it is labour-intensive and expensive involving handling of live virus and requires standardised reagents that often are not available [83, 84].

Viral Isolation~~; this~~ is used to isolate the virus from body fluids and tissue, ~~It is the gold standard for virus~~ Virus isolation remains the gold standard but requires (more laboratory infrastructure?) for cell culture [85]. When using ELISA and PRNT, the major limitation is the cross-reactions with a previous history of flavivirus infection or immunization against another Flavivirus [4, 83, 85].

(Discuss the sensitivity, specificity, PPV, NPV and accuracy of these tests)

(The CDC has issued interim guidance on Zika virus antibody testing and interpretation, as follows:

Serum IgM testing should be performed if real-time RT-PCR (rRT-PCR) results are negative, notwithstanding when the specimen was collected.

A 4-fold higher titer based on plaque reduction neutralization test (PRNT) results might not differentiate anti-Zika virus antibodies from cross-reacting antibodies in all persons with previous infection or vaccination against a related flavivirus.

If IgM testing is positive for Zika or dengue virus or returns equivocal results, the following PRNT interpretations apply:

A PRNT titer >10 indicates evidence of infection with that specific flavivirus when the PRNT to the other flavivirus(es) tested is < 10.

A PRNT titer < 10 to a specific flavivirus indicates an absence of infection with that virus.

A positive PRNT result (>10 to multiple flaviviruses) indicates evidence of recent flaviviral infection.

All pregnant women should be screened for a travel history to Zika virus–affected areas. Symptomatic pregnant women with a positive travel history should undergo RT-PCR or serological testing for detection of Zika virus infection.

All pregnant women with a history of travel to an area of active Zika virus infection should undergo fetal ultrasonography to evaluate for microcephaly or intracranial calcifications. Detection of a fetal anomaly should be followed by amniocentesis for evaluation of intrauterine Zika virus infection.)

## 8. TREATMENT AND MANAGEMENT (It is best to limit the article to the Epidemiology including Transmission, Control & Prevention beside Diagnosis including Laboratory-diagnosis, leaving out clinical-management)

Treatment is focused mainly on supportive care and management of symptoms as there is no known treatment available for ZIKV infection or some of its complications. [4]. ZIKV infection can often be asymptomatic, but when symptoms are present, they are usually mild. Symptoms such as fever, rash, or arthralgia are managed with plenty of rest, staying well hydrated by drinking plenty of fluids [86]. Pain and fever are treated with NSAIDs (What about simple non-NSAID analgesics and anti-pyretics?) ; however, diagnosis of Dengue fever should first be ruled out to avoid hemorrhage associated with the use of NSAIDs when ill with dengue. If symptoms worsen, further medical care should be considered [87]. Aspirin is contraindicated for use in children below the age of 12 years due to the risk of Reye syndrome [88]. Pregnant women with fever should be treated with acetaminophen [57, 89]. Antihistamines may also be prescribed for an itchy rash [87]. Pregnant women in areas with ongoing Zika transmission or who develop symptoms of ZIKV infection should seek prompt medical attention for laboratory testing and additional clinical care. Consultation with an experienced obstetrics and gynecology specialist in conjunction with an infectious disease specialist is vital in the management of possible ZIKV infection [89]. Some of the care includes repeated ultrasonography for fetal evaluation, amniocentesis, postnatal management in the testing of placental tissues, and newborns should be tested and evaluated for congenital ZIKV infection in accordance with CDC guidelines [57, 86]. Follow-up care of children born to mothers with probable exposure to ZIKV during pregnancy is critical for appropriate intervention [86].

## 9. PREVENTION

There are several DNA vaccines currently at different phases of trials in the hope of using prevention as the main alternative to combat the disease [90]. (Discuss vaccine-development in greater detail, including cost-benefit.) The current WHO strategic Response plan recommends Community engagement, integrated vector management, and Public health risk communication to aid the prevention of Zika adverse outcomes [91]. Currently, avoiding mosquito bites is critical in endemic regions and places with active outbreaks, or where Aedes species mosquitoes are active. The community should be involved in community drives such as the elimination of mosquito breeding sites, and aim towards control of the vector. Wearing long-sleeved clothes and pants to cover as much of the body as possible, and use of mosquito repellents when outdoors (why only outdoors?) is recommended [91]. (What about the use of insecticides, laervicides, and ovitraps – including the routine and regular use of effective and safe household insecticide sprays? Families could greatly benefit from community-education in the use of these and mosquito-repellents/mosquito-nets. What about governments and NGOs providing these to outbreak areas, perhaps in a subsidized manner?) Use of window and door screens when indoors is essential in areas of mosquito transmission (How effective is such?) . Pregnant women and children should also sleep under mosquito nets if sleeping during the day or early evening. Sexually active men and women, as well as pregnant women, should practice safe sex with the correct use of condoms. During ZIKV outbreaks, couples should be counselled and offered a full range of contraceptive methods after considering potential adverse pregnancy and fetal outcomes of ZIKV [57].

## 10. COMPLICATIONS AND OUTCOMES OF ZIKV INFECTION

Usually, Zika fever clears on its own in 2 to 7 days, and rarely (exact incidence?), some people develop Guillain–Barré syndrome (GBS) [4]. However, Zika fever, especially during the first trimester, has severe effects on the fetus, such as miscarriages and increases the risk of congenital disabilities [2, 4], for example, ~~a baby~~ infants born with congenital central nervous system deformities [7]. It is also associated with other complications of pregnancy, including IUGR (intrauterine growth retardation), preterm birth, stillbirth, eye abnormalities, and neonatal death [47].

Microcephaly, the most typical form of ZIKV related birth defects, is often associated with developmental delays as well as intellectual, visual, and hearing impairment and epilepsy [7,68]. Recent studies indicate that the risk of ZIKV related congenital disabilities is the same whether the pregnant woman experiences symptoms on ZIKV infection or not [57, 92]. Considerable evidence has linked GBS to ZIKV infection, a condition resulting from neurological damage (inflammation of the brain and spinal cord) [7, 93]. GBS (Is GBS self-limiting, treatable, not-treatable or protracted/chronic?) patients are reported to usually present with bilateral paresthesias, peripheral muscle weakness, and facial palsy [93]. Besides, ZIKV infection in older children and adults may lead to other neurological conditions such as encephalomyelitis, acute myelitis, encephalitis, meningoencephalitis, and sensory polyneuropathy [93, 94].

Complications of ZIKV in Africa are less documented, and its outcomes had been undetected [95] not until the recent outbreaks outside Africa that drew more attention to ZIKV complications and outcomes in Africa. In the 2016 Cabo Verde (Where is Cabo Verde?) outbreak, 50% of confirmed microcephaly cases were linked to ZIKV infection. [52], and the first

case (just the first case now?) of congenital Zika syndrome in Africa was recently reported in 2018, in a newborn from Angola [96].

## 11. CONCLUSION

ZIKV being a disease relatively silent because of its asymptomatic nature and lesser-known outcomes on the continent, calls for a targeted response for its early detection, prevention, care, and support of affected populations. Despite its origin in Africa, there is still limited information on the Trends, distribution, and transmission of ZIKV in Africa due to a lack of awareness and weak surveillance mechanisms. Thus there is considerable potential for future outbreaks in the continent especially in regions without herd immunity posing an enormous global health challenge if it is not addressed. There is a need to develop cost-effective and easy to use diagnostic tests for prompt detection of ZIKV in endemic regions. Without medical development such as a vaccine, or unique pest control, Zika seems destined to start spreading again in African countries. In addition, more research on the missing gaps is required as well as Policy strengthening, especially on refugee surveillance. Never the less the current efforts in developing new vaccines have provided hope for better prevention and control of the virus

## ~~CONSENT~~

~~It is not applicable.~~

## ~~ETHICAL APPROVAL~~

~~It is not applicable.~~

## COMPETING INTERESTS

Authors declare that no competing interests exist.

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