

ZIKA VIRUS



*Cattelya Orchid and Three Brazilian Hummingbirds*”, oil on canvas, 1871.  
Martin Johnson Heade

*“Nature everywhere speaks too humanity in a voice that is familiar to the soul”*

*Alexander von Humboldt, (1769- 1859).*

*Alexander von Humboldt has been largely forgotten in the English-speaking world. He was one of the last polymaths, and died at a time when scientific disciplines were hardening into tightly fenced and more specialized fields. Consequently his more holistic*

*approach- a scientific method that included art, history, poetry and politics alongside hard data - has fallen out of favor. By the beginning of the twentieth century, there was little room for a man whose knowledge had bridged a vast range of subjects. As scientists crawled into their narrow areas of expertise, dividing and further subdividing, they lost Humboldt's interdisciplinary methods and his concept of nature as a global force.*

*One of Humboldt's greatest achievements had been to make science accessible and popular. Everybody learned from him: farmers and craftsmen, schoolboys and teachers, artists and musicians, scientists and politicians. There was not a single textbook or atlas in the hands of children in the western world that hadn't been shaped by Humboldt's ideas, one orator had declared during the 1869 centennial celebrations in Boston. Unlike Christopher Columbus or Isaac Newton, Humboldt did not discover a continent or a new law of physics. Humboldt was not known for any one single fact or a discovery but for his worldview. His vision of nature has passed into our consciousness as if by osmosis. It is almost as though his ideas have become so manifest that the man behind them has disappeared.*

*Another reason why Humboldt has faded from our collective memory - at least in Britain and the United States (and Australia and New Zealand) - is the anti-German sentiment that came with the First World War. In a country such as Britain, where even the royal family felt that they had to change their German sounding surname "Saxe-Coburg-Gotha", to "Windsor", and where the works of Beethoven and Bach were not played anymore, it is hardly surprising that a German scientist was no longer popular. Similarly in the United States, when Congress joined the conflict in 1917, German - Americans were suddenly lynched and harassed. In Cleveland, where fifty years earlier thousands had marched through the streets in celebration of Humboldt's centennial, German books were burned in a large bonfire. In Cincinnati all German publications were removed from the shelves of the public library and "Humboldt Street" was renamed "Taft Street". Both world wars of the Twentieth century cast long shadows, and neither Britain nor America were places for the celebration of a great German mind any more.*

*So why should we care?...There are several answers to the question because there are many reasons why Humboldt remains fascinating and important: not only was his life colorful and packed with adventure, but his story gives meaning to why we see nature the way we see it today. In a world where we tend to draw a sharp line between the sciences and the arts, between the subjective and the objective, Humboldt's insight that we can only truly understand nature by using our imagination makes him a visionary.*

*Humboldt's disciples, and their disciples in turn, carried his legacy forward - quietly, subtly and sometimes unintentionally. Environmentalists ecologists and nature writers today remain firmly rooted in Humboldt's vision - although many have never heard of him. Nonetheless, Humboldt is their founding father.*

*As scientists are trying to understand and predict the global consequences of climate change, Humboldt's interdisciplinary approach to science and nature is more relevant than ever. His beliefs in the free exchange of information, in uniting scientists and in fostering communication across disciplines, are the pillars of science today. His concept of nature as one of global patterns underpins our modern thinking....*

*Just as Humboldt realized that colonies based on slavery, monoculture and exploitation created a system of injustice and of disastrous environmental devastation, so we too have to understand that economic forces and climate change are all part of the same system.*

*Humboldt talked of “mankind’s mischief...which disturbs nature’s order”. There were moments in his life when he was so pessimistic that he painted a bleak future of humankind’s eventual expansion into space, when humans would spread their lethal mix of vice, greed, violence and ignorance across other planets. The human species could turn even more distant stars “barren” and leave them ravaged, Humboldt wrote as early as 1801, just as they were already doing with the Earth.*

*It feels as if we have come full circle. Maybe now is the moment for us and for the environmental movement to reclaim Alexander von Humboldt as our hero.*

*Goethe compared Humboldt to a “fountain with many spouts from which streams flow refreshingly and infinitely, so that we only have to place vessels under them”.*

*That fountain, I believe, has never run dry.*

*Andrea Wulf, The Invention of Nature”, Knopf, 2015.*

*The brilliant German Naturalist, and polymath, Alexander von Humboldt, by his grand explorations on the Amazon and the Orinoco in South America, came to understand the environment in a very modern way - indeed in his thinking he was almost two centuries ahead of his time. The world and all of nature are inextricably linked, in the most beautiful and yet fragile ways. He despaired at the destruction of the environment wreaked by humankind, in an age that had not the slightest concept of environmental sciences. Indeed he even surmised that if humanity ever reached the stars - they would invariably wreak the very same havoc on any pristine worlds that may orbit them - a uniquely prescient thought in the setting of the early Nineteenth century. In many ways, as the magisterial Andrea Wulf has described, he can be considered the father of modern environmentalism, even though today he is hardly known - perhaps in part a legacy, of the world conflicts of the Twentieth century that suppressed the memory of his brilliant work, outside of his native Germany.*

*In the 21st century, the world is interconnected in more ways than Alexander (the father of environmentalism) - or indeed anyone of his time - could have possibly imagined. Modern aviation, shipping and communication technologies, now connect human societies within an immense “global village”. Alexander and all other intrepid explorers once greatly feared exotic infectious diseases in the distant lands they travelled to. The havoc humanity increasingly wreaks on the fragile environment now sees the distinct possibility of a generalized global warming. Modern transportation sees the rapid dissemination of once geographically restricted diseases. But with global warming another even more sinister possibility awaits us. Ecosystems in the next centuries to come may be radically altered and topical species will increasingly be found in regions where previously they had not existed - and with them may also come diseases that are today far more regionally restricted.*

## ZIKA VIRUS



*The Aedes aegypti mosquito (US Dept of Health and Human Services).*

### Introduction

**Zika virus** is an emerging **arbovirus** (or arthropod - in this case - mosquito-borne) flavivirus transmitted primarily by **Aedes aegypti** and **Aedes albopictus** mosquitoes. These vectors also transmit **dengue** and **chikungunya virus**.

About 80% of cases are subclinical.

Clinical disease is usually mild with symptoms lasting for several days to a week.

Clinical features are similar to those of **dengue** and **chikungunya**, diseases spread through the same mosquitoes that transmit Zika. **Note that coinfection with these viruses is also possible.**

Severe disease requiring hospitalization is uncommon. Deaths are rare.

However two important complications have been recognized:

1. **Guillain-Barre syndrome:**

- There have been cases of **Guillain-Barre syndrome** reported in patients following outbreaks of Zika virus infection.

## 2. **Birth Defects:**

The Brazil Ministry of Health is also investigating the possible association between Zika virus and a reported increase in the number of **babies born with microcephaly**.

Due to concerns of microcephaly associated with maternal Zika virus infection, fetuses and infants **of women infected with Zika virus during pregnancy** should be evaluated for possible **congenital infection** and **neurologic abnormalities**.

There is no vaccine available and no specific antiviral medication is available and so treatment is supportive.

**Cases have been reported in returning travelers from endemic regions.**

Imported cases could result in local spread of the virus in regions that have the **Aedes species mosquito**.

**Health care providers should ask all pregnant women about recent travel. Women who traveled to an area with ongoing Zika virus transmission during pregnancy should be evaluated for Zika virus infection and/ or its complications.**

## History<sup>3,5</sup>

With the exception of West Nile virus, which is predominantly spread by culex-species mosquitoes, the arboviruses that recently reached the Western Hemisphere have been transmitted by aedes mosquitoes, especially the yellow fever vector mosquito *A. aegypti*.

These viruses started to emerge millennia ago, when North African villagers began to store water in their dwellings. Arboreal

*A. aegypti* then adapted to deposit their eggs in domestic water containing vessels and to feed on humans, which led to adaptation of arboreal viruses to infect humans.

The yellow fever, dengue, and chikungunya viruses evolved entirely new maintenance cycles of human - *A. Aegypti* - human transmission. Now, 5000 years later the worst effects of this evolutionary cascade are being seen in the repeated emergence of arboviruses into new ecosystems involving humans. Moreover, arboviruses transmitted by different mosquitoes have, in parallel, adapted to humans' domestic animals, such as horses in the case of Venezuelan equine encephalitis and pigs in the case of Japanese encephalitis virus, or to vertebrate hosts and non-aedes mosquitoes found in areas of human habitation, as West Nile virus did.

**Zika virus** was first isolated from a rhesus monkey in Zika forest, Uganda in 1947, in mosquitoes (*Aedes africanus*) in the same forest in 1948 and in humans in Nigeria in 1954.

Zika virus is endemic in parts of Africa and Asia and was first identified in the South Pacific after an outbreak on Yap Island in the Federated States of Micronesia in 2007.

As of 2015, the virus has been rapidly spreading via mosquitoes in South America and Central America. The explosive pandemic of Zika virus infection occurring throughout South America, Central America, and the Caribbean and potentially threatening the United States is the most recent of four unexpected arrivals of important arthropod-borne viral diseases in the Western Hemisphere over the past 20 years.

It follows **dengue**, which entered the western hemisphere stealthily over decades and then more aggressively in the 1990s; **West Nile virus**, which emerged in 1999; and **chikungunya**, which emerged in 2013.

It is currently uncertain whether the successive migrations of these viruses are unrelated, or whether they reflect important new patterns of disease emergence.

### Epidemiology

Prior to 2015, Zika virus outbreaks have occurred in areas of Africa, Southeast Asia, and the Pacific Islands.

In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infections in Brazil

Zika virus will continue to spread and at this time it is difficult to predict how the virus will spread over time.

**Cases have been reported in returning travelers from endemic regions.**

Imported cases could result in local spread of the virus in regions that have the **Aedes species mosquito**.

In Australia **Aedes aegypti** is found in **far north Queensland** and **Aedes albopictus** has a possible geographical distribution that extends down the east coast of Australia.

### Pathology

#### Organism

**Zika virus** is a single stranded RNA virus of the genus **Flavivirus** in the Flaviviridae family.

## Transmission

Transmission can be via:

1. Mosquito bites:

- Zika virus is transmitted to people primarily through the bite of an infected **Aedes species mosquito**.

It is *primarily* transmitted by **Aedes aegypti**, but *Aedes albopictus* mosquitoes can also transmit the virus.

**Aedes aegypti** and **Aedes albopictus** are the same mosquitoes that spread **dengue** and **chikungunya** viruses.

These mosquitoes typically lay eggs in and near standing water in things like buckets, bowls, animal dishes, flower pots and vases.

They are aggressive daytime biters, prefer to bite people, and live indoors and outdoors near people.

Mosquitoes become infected when they feed on a person already infected with the virus. **Viremia persists for about 1 week**.

Infected mosquitoes can then spread the virus to other people through bites.

2. From mother to child:

- A mother already infected with Zika virus near the time of delivery can pass on the virus to her newborn around the time of birth, but this is uncommon.

Maternal-fetal transmission of Zika virus has also been documented throughout pregnancy.<sup>2</sup>

To date, there are no reports of infants getting Zika virus through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed even in areas where Zika virus is found.

3. Possibly through infected blood or sexual contact:

- There has to date been one report of possible spread of the virus through blood transfusion and several reports of possible spread of the virus through sexual contact.

Zika virus RNA has been identified in asymptomatic blood donors during an ongoing outbreak.

### Incubation Period

- The incubation period for Zika virus disease is unclear, but is likely to be of the order of 2 - 7 days.

### Reservoir

- Non-human and human primates are likely the main reservoirs of the virus, and anthroponotic (human-to-vector-to-human) transmission can occur during outbreaks.

### Period of Communicability

- During the first week of infection, Zika virus can be found in the blood and passed from an infected person to another mosquito through mosquito bites.

An infected mosquito can then spread the virus to other people

### Susceptibility and Resistance

- Presumably all are susceptible.

### Clinical Features

An estimated 80 % of persons infected with Zika virus have a subclinical infection (i.e they are asymptomatic).

Clinical illness is usually mild with symptoms lasting for several days to a week.

Severe disease requiring hospitalization is uncommon.

Deaths are rare.

Clinical features are similar to those of **dengue** and **chikungunya**, although generally milder in severity. **Dengue** and **chikungunya** are diseases spread through the same mosquitoes that transmit Zika.

**Health care providers should ask all pregnant women about recent travel. Women who traveled to an area with ongoing Zika virus transmission during pregnancy should be evaluated for Zika virus infection.**

Clinical features include:

1. Fever (low grade):
  - May **not** be present (possibly only around one third of cases).<sup>6</sup>

2. Non-specific constitutional symptoms:
  - Headache
  - Myalgias
  - Arthralgias
3. Maculopapular rash (see Appendix 3 below).
  - May be (or may not be) pruritic.
4. Lymphadenopathy
5. Conjunctivitis (non-purulent)/ conjunctival injection.

Complications:

Two important complications have been recognized:

1. **Guillain-Barré syndrome:**

- There have been cases of **Guillain-Barre syndrome** reported in patients following suspected Zika virus infection.

2. **Birth Defects:**

The Brazil Ministry of Health is also investigating the possible association between Zika virus and a reported increase in the number of **babies born with birth defects**.

**Pregnancy related complications** have included:

- **CNS defects (microcephaly in particular)**
- **Fetal death**
- **Fetal growth restriction**
- **Placental insufficiency**

Due to concerns of microcephaly associated with maternal Zika virus infection, fetuses and infants **of women infected with Zika virus during pregnancy** should be evaluated for possible **congenital infection** and **neurologic abnormalities**.

**The risk of microcephaly is greatest during the first trimester.**

No evidence exists to date to suggest that pregnant women are more susceptible or experience more severe disease during pregnancy.

It is not known if pregnant women are more susceptible to Guillain-Barré syndrome.

## Investigations

### Serology:

Both **IgG** and **IgM** antibodies can be detected.

Acute serum (taken within 5 days of symptom onset) and convalescent serum (2 - 3 weeks later) should be taken. The two samples are important to rule out false positive tests due to cross reactivity with similar viruses such as Dengue

Virus-specific IgM and neutralizing antibodies typically develop toward the end of the first week of illness.

Cross-reaction with related **flaviviruses** (e.g., **dengue** and **yellow fever viruses**) is common and may be difficult to discern from Zika virus.

Plaque-reduction neutralization testing (PRNT) can be performed to measure virus-specific neutralizing antibodies to confirm primary flavivirus infections and differentiate from other viral illnesses

### PCR testing:

During the **first week** after onset of symptoms, Zika virus disease can often be diagnosed by performing reverse transcriptase-polymerase chain reaction (**RT-PCR**) on **serum** and/or **on urine**.

**The virus is detectable in blood during the period of acute viremia and initial symptoms and subsequently is shed in the urine, generally for 3 to 14 days.**<sup>6</sup>

RT-PCR test may not demonstrate Zika virus RNA in a woman with Zika virus infection if the period of viremia has passed. Serum serologic testing will be needed in these cases.

### Amniocentesis:

Zika virus RT-PCR testing can be performed on amniotic fluid.

Currently, it is unknown how sensitive or specific this test is for congenital infection.

Also, it is unknown if a positive result is predictive of a subsequent fetal abnormality, and if so, what proportion of infants born after infection will have abnormalities.

### Co-infection:

Because of similar geographic distribution and symptoms, patients with suspected Zika virus infections should also be evaluated and managed for possible:

- **Dengue virus infection.**
- **Chikungunya virus infection.**
- **Malaria**

### Management

#### Prevention:

Because there is neither a vaccine nor prophylactic medications available to prevent Zika virus infection, it is recommended that all pregnant women consider postponing travel to areas where Zika virus transmission is ongoing; particularly during the first trimester when the risk of microcephaly is greatest.

If a pregnant woman travels to an area with Zika virus transmission, she should be advised to strictly follow steps to avoid mosquito bites.

Men who have travelled to areas with ongoing Zika virus transmission whose partner is pregnant should abstain from sexual activity (vaginal, anal, or oral) or consistently use condoms for the duration of the pregnancy, whether symptomatic or asymptomatic.<sup>4</sup>

Men who have had a confirmed Zika virus infection, whose partner is not pregnant should abstain from sexual activity (vaginal, anal, or oral) or consistently use condoms for 3 months following the resolution of symptoms.<sup>4</sup>

#### Supportive:

There is no specific therapy available and so treatment is supportive.

Fever should be treated with **paracetamol**.

**Aspirin** and other **NSAIDs** should be **avoided** until **dengue** can be ruled out to reduce the risk of hemorrhage.

A suggested algorithm for managing pregnant woman with possible exposure to the Zika virus has been developed by the CDC, (see **Appendix 2 below**).

#### Vaccination

- There is no current vaccine available for the Zika virus.

Notification:

- Any case of Zika Virus infection must (like other flaviviruses) be notified to the relevant State Health Department authorities.

## Appendix 1



*Countries with Past or Current Evidence of Zika Virus Transmission (as of December 2015).*

*For countries with serosurvey data only, evidence of Zika virus transmission is derived from studies that detected Zika virus antibodies in healthy people. Outlined areas, all with locally acquired cases or virus isolation, include Cape Verde, Cook Islands, Easter Island, Federated States of Micronesia, French Polynesia, Martinique, New Caledonia, Puerto Rico, Solomon Islands, and Vanuatu, (CDC Website).*



### Appendix 3

#### Rash associated with Zika Virus: <sup>6</sup>



*Panel A:* A maculopapular rash on the face.

*Panel B:* Conjunctival and palpebral erythema.

*Panel C:* Retroauricular lymphadenopathy.

*Panel D:* Conjunctival injection with prominence of vasculature.



*Panel E:* A rash on the legs, with a lacy reticular pattern.

*Panel F:* A maculopapular rash on the inner arm.

*Panel G:* Edema of the foot, which the patient reported was painful.

*Panel H:* A blanching macular rash on the gravid abdomen.



*Alexander von Humboldt (left) and Aime Bonpland, oil on canvas, in Brazil, 1856, Eduard Ender.*

## References

1. Zika Virus in CDC Website January 2016.
2. Emily E. Petersen, J. Erin Staples et al. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak United States, 2016:  
  
MMWR January 22, 2016, Vol. 65, No. 2 US Department of Health and Human Services/Centers for Disease Control and Prevention
3. Zika Virus Fact Sheet; WHO Website, January 2016.
4. Interim Guidelines for Zika Virus ACEM Summary Statement, February 2016.
5. A. S. Fauci and D.M. Morens. Zika Virus in the Americas - Yet Another Arbovirus Threat. NEJM 374 (7) 18 February 2016.
6. Patricia Brasil et al, Zika Virus Infection in Pregnant Women in Rio de Janeiro - Preliminary Report. NEJM 4 March 2016.
  - DOI: 10.1056/NEJMoa1602412.

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