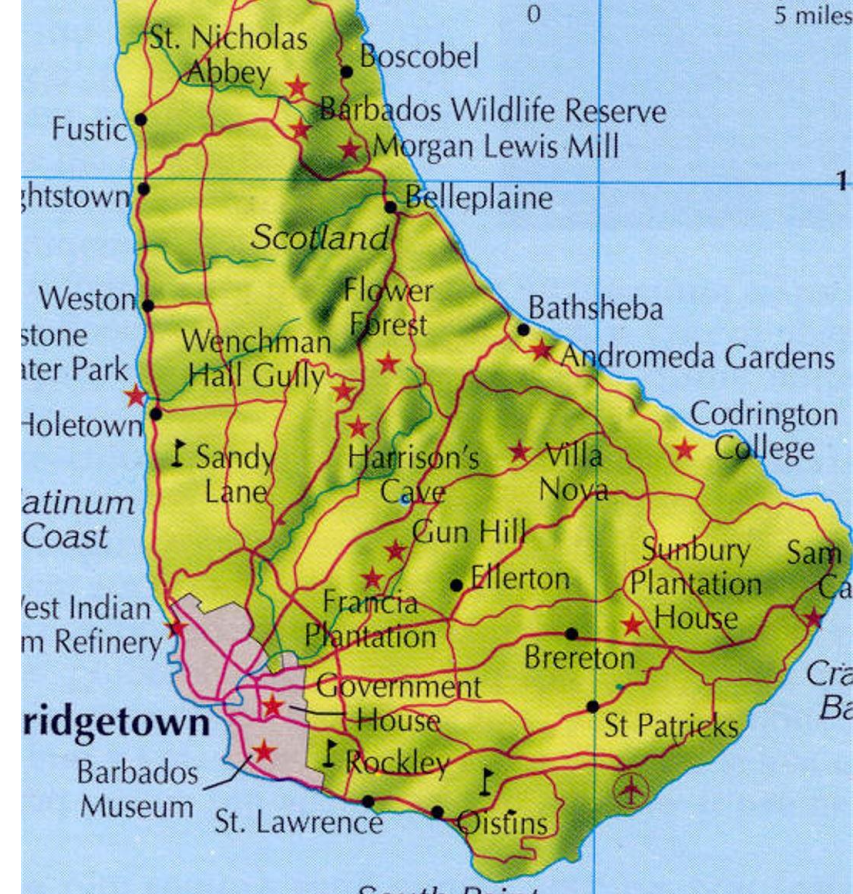




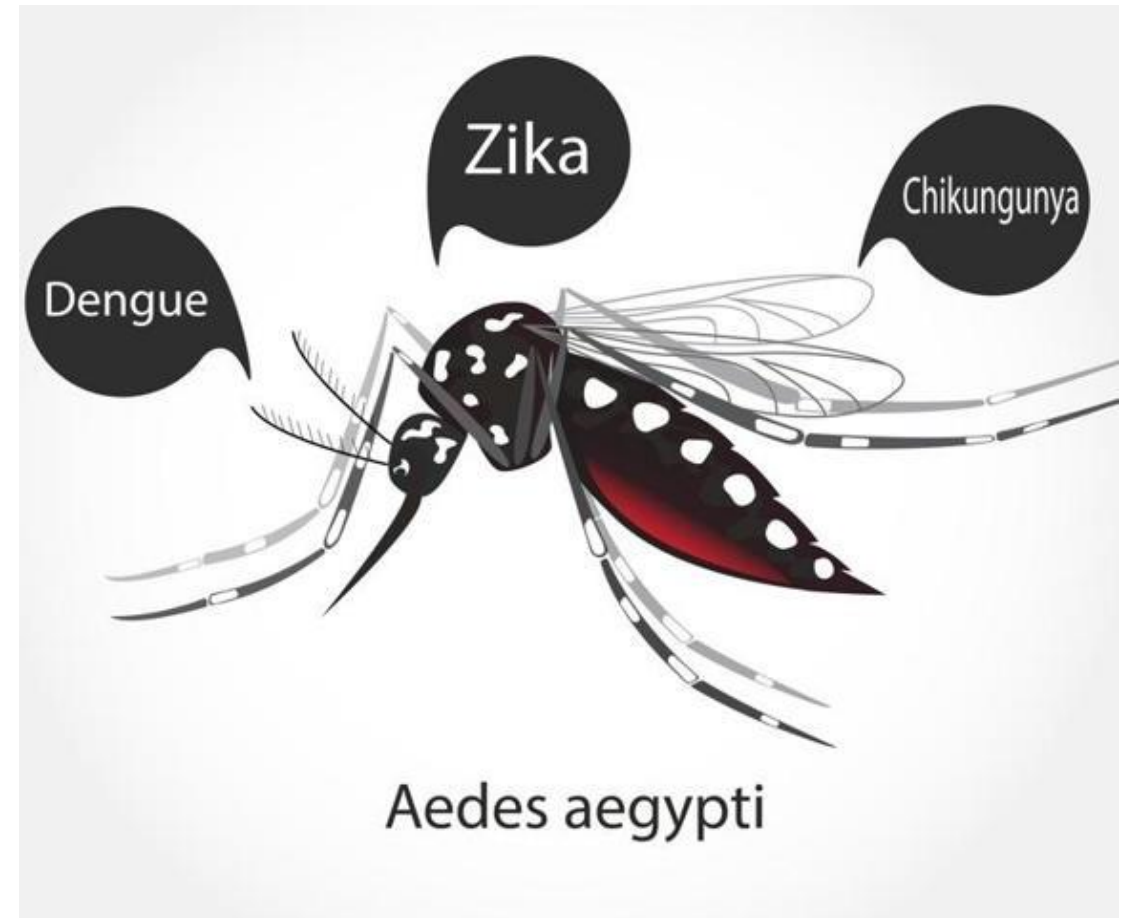
OCULAR MANIFESTATIONS OF MOSQUITO-BORNE DISEASES

MR Kevin Highland MBBS MRCOphth FRCS(Glasgow)



INTRODUCTION

- **Dengue, chikungunya and zika viruses** have emerged as increasingly important causes of human disease.
- **Ocular manifestations** of these diseases have become more prevalent over the past few years.
- This review highlights the current understanding of the ocular findings, emphasizing the retinal manifestations related to these diseases.



INTRODUCTION

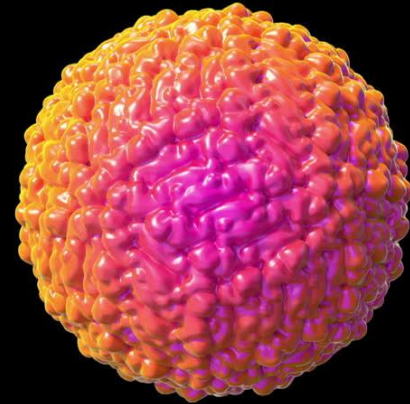
Arbovirus (ARthropod-
BOrne virus)



Flavivirus:
Dengue
Zika



Alphavirus:
chikungunya

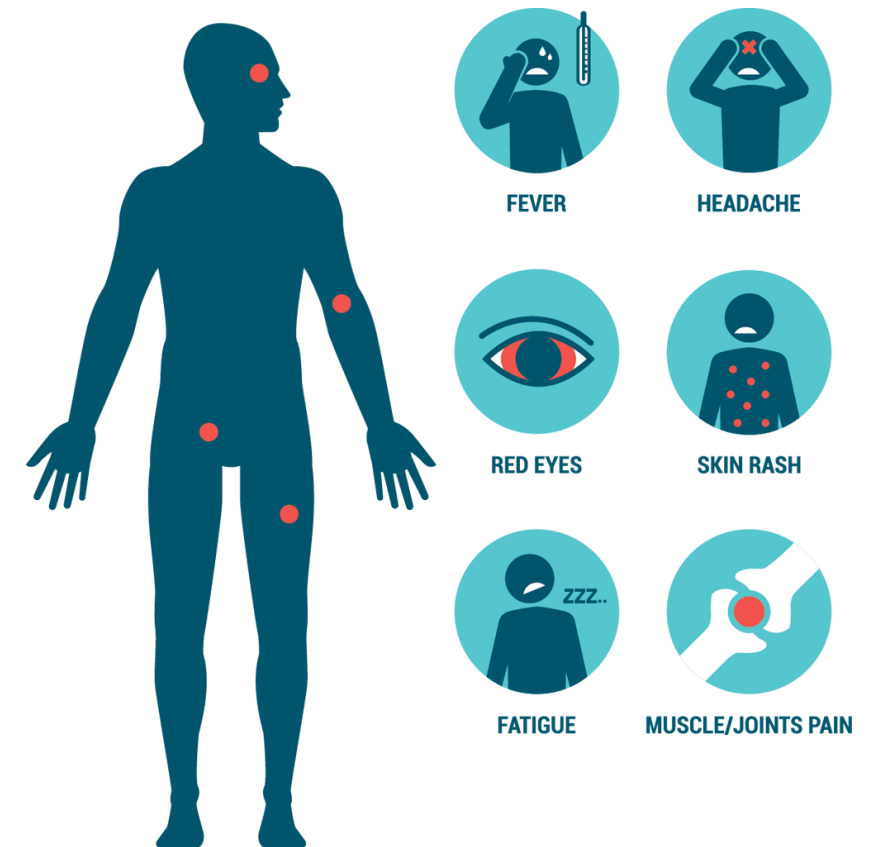


- **Arbovirus** is a term used to refer to any virus that is transmitted by an **arthropod** vector.
- Differ in size, morphology, gene sequence and replication.



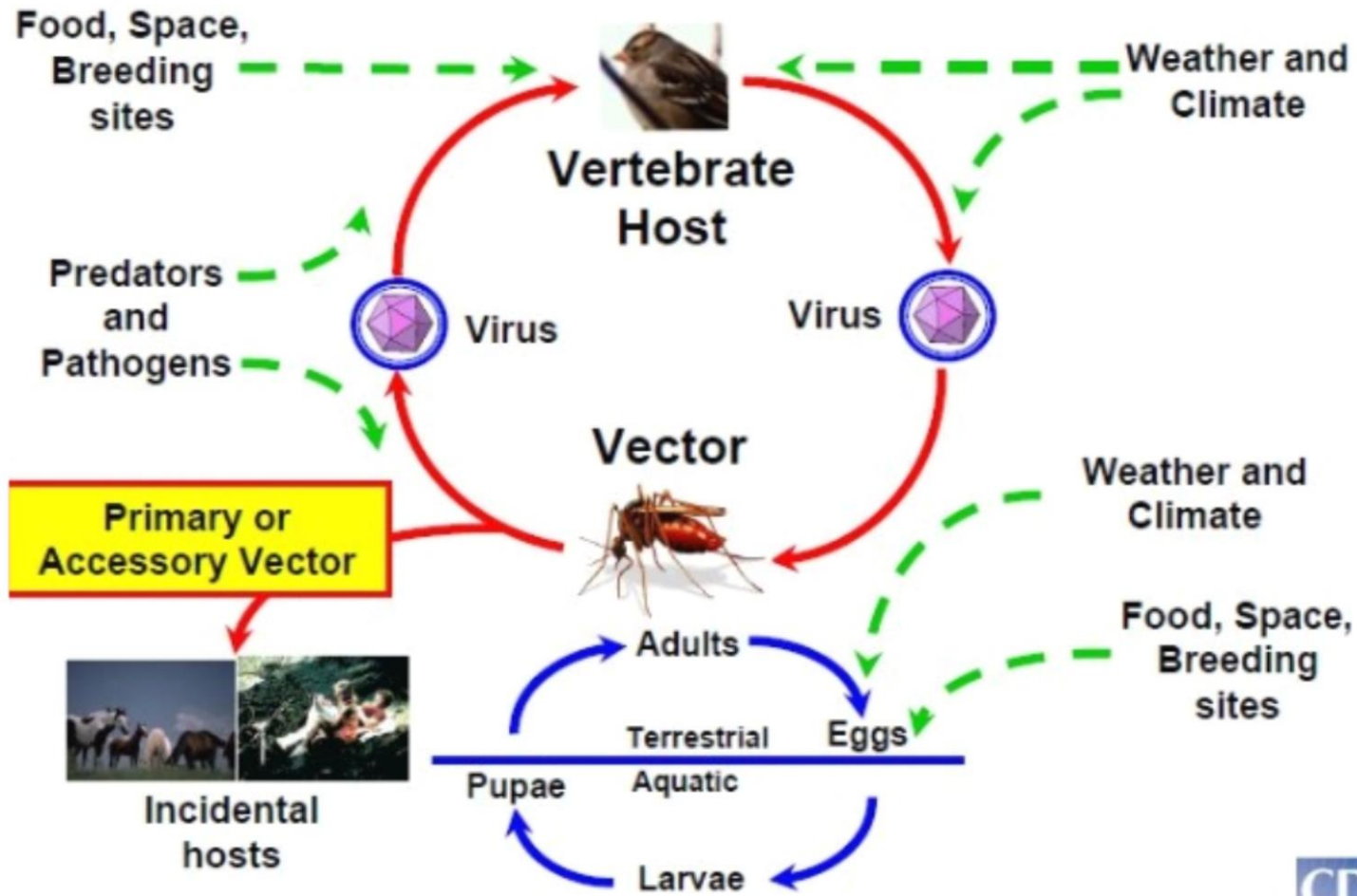
INTRODUCTION

- Vector borne diseases account for over 17% of all infectious diseases, causing more than 1 million deaths annually.
- The illnesses caused by the arboviruses have very similar clinical presentation with prominent fever, headache, rash, myalgia and arthralgia.
- In fact, serologic surveys have demonstrated that outbreaks attributed to **DENGUE** in the past have actually turned out to be **CHIKV** or **ZIKV** infections.



INTRODUCTION

Arbovirus Transmission Cycle



- **Globalization** of travel and trade, unplanned urbanization and environmental challenges such as **climate change** are having a significant impact on disease transmission.

SOME MAIN VECTORS AND DISEASES THEY TRANSMIT



Vectors

Main diseases

Aedes Aegypti

Dengue fever
Zika virus
Rift valley fever
Yellow fever
Chikungunya

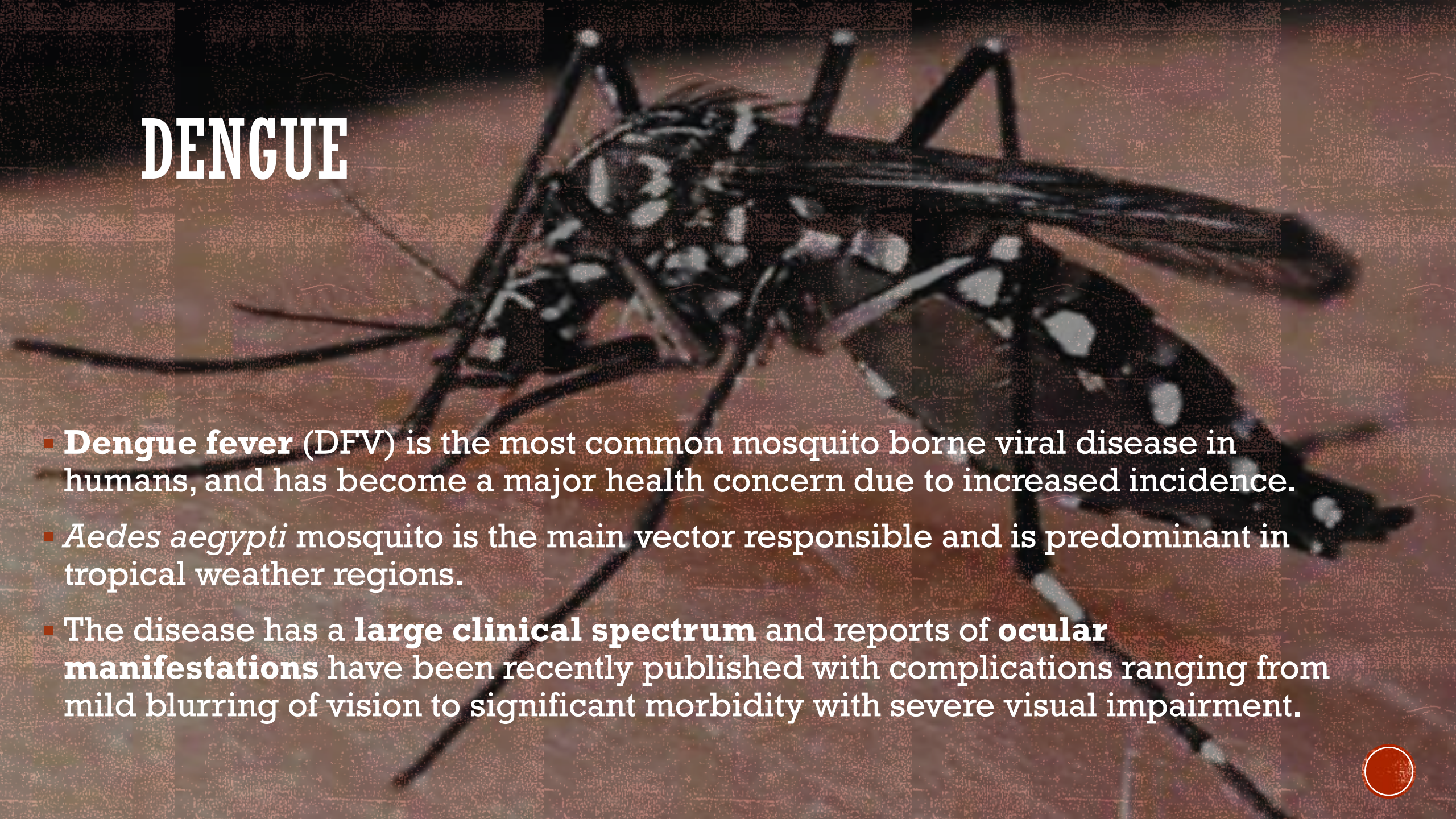
Anopheles

Malaria
Lymphatic filariasis

Culex

Japanese encephalitis
Lymphatic filariasis
West Nile fever

DENGUE



- **Dengue fever** (DFV) is the most common mosquito borne viral disease in humans, and has become a major health concern due to increased incidence.
- *Aedes aegypti* mosquito is the main vector responsible and is predominant in tropical weather regions.
- The disease has a **large clinical spectrum** and reports of **ocular manifestations** have been recently published with complications ranging from mild blurring of vision to significant morbidity with severe visual impairment.



DENGUE FEVER

- Dengue infection is characterized by an acute onset of fever associated with symptoms of malaise, sore throat, rhinitis and cough, headache, muscle ache, retro-orbital pain, joint pain, abdominal discomfort, and rash.
- Other clinical manifestations of dengue are related to the bleeding diathesis from thrombocytopenia.
- Infection is caused by the dengue virus, of which there are **four** closely related but antigenically distinct serotypes that **do not** confer cross-immunity.
- As such, individuals in endemic countries are not protected from the other serotypes after infection with one serotype.



INVESTIGATIONS

DIAGNOSIS FOR DENGUE FEVER



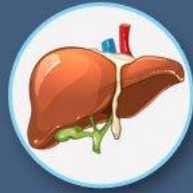
Complete
blood
count



PCR Test
(Polymerase
Chain
Reaction)



Antibody
titer for
dengue
virus type



Liver
function
test

- Dengue infection is usually a clinical diagnosis but can be confirmed with lab tests based on the time of presentation.
- Frequently used tests include PCR, and IgM or IgG enzyme immunoassays .
- During the early phase of the infection, when febrile illness is within 5 days, dengue PCR is performed.
- If febrile illness exceeds 5 days, the preferred tests are dengue IgM and IgG tests.



PATHOPHYSIOLOGY

- The precise pathophysiologic mechanism of dengue ophthalmic complications is not well understood; however, many studies have alluded to the possibility of an **immune-mediated** process as a likely mechanism.
- Ocular finding usually present 4-5 days after onset of fever.



OPHTHALMIC SYMPTOMS OF DENGUE-RELATED COMPLICATIONS

■ **Blurring of Vision**

- The most common complaint was blurring of vision.
- In three case series involving 23 patients, all of them complained of blurring of vision with visual acuity decreasing to counting fingers in two of the studies.



OPHTHALMIC SYMPTOMS OF DENGUE-RELATED COMPLICATIONS

- **Scotoma**
- The next most common symptom was **central scotoma**.
- The areas of **scotoma** generally corresponded to the areas of **oedema** and **haemorrhage** in the macula.
 - In the case series by Chan et al. (2006) 12 out of 13 patients had central scotoma in association with blurring of vision.



OPHTHALMIC SYMPTOMS OF DENGUE-RELATED COMPLICATIONS

- **Ocular Pain**
- Usually associated with headache.
- Location of the pain is typically described as retrobulbar and worse on eye movements.*

***Headache features in patients with dengue virus infection.**

Domingues RB¹, Kuster GW, Onuki de Castro FL, Souza VA, Levi JE, Pannuti CS.





OCULAR COMPLICATIONS INVOLVING THE ANTERIOR SEGMENT OF THE EYE

■ Subconjunctival Haemorrhage

- A study by Kapoor et al. accounted for the majority of cases of dengue-related subconjunctival haemorrhage.
- 134 patients hospitalized with a diagnosis of dengue fever during an epidemic were included.
- 50 patients had subconjunctival haemorrhage, 42 (84%) patients had petechial haemorrhages present in the conjunctivae and eight (16%) patients had diffuse haemorrhages noted in one to four quadrants.
- Of all lab parameters evaluated, **marked thrombocytopenia** emerged to be significantly associated with ocular haemorrhage.



OCULAR COMPLICATIONS INVOLVING THE ANTERIOR SEGMENT OF THE EYE

■ Uveitis

- Patients with dengue infection rarely presented with uveitis.
- A case series by Gupta et al. reported dengue-related uveitis in six patients, The pts presented with ocular symptoms **3-5 months after contracting dengue fever** without any other attributable cause for uveitis.*
- They were treated with topical steroids, cycloplegic, and ocular hypotensive medications, when required, and oral steroid in case of posterior segment involvement.
- **We should be aware of the delayed ophthalmic complications of dengue infection like uveitis, which might occur even after complete recovery from the systemic disease.**

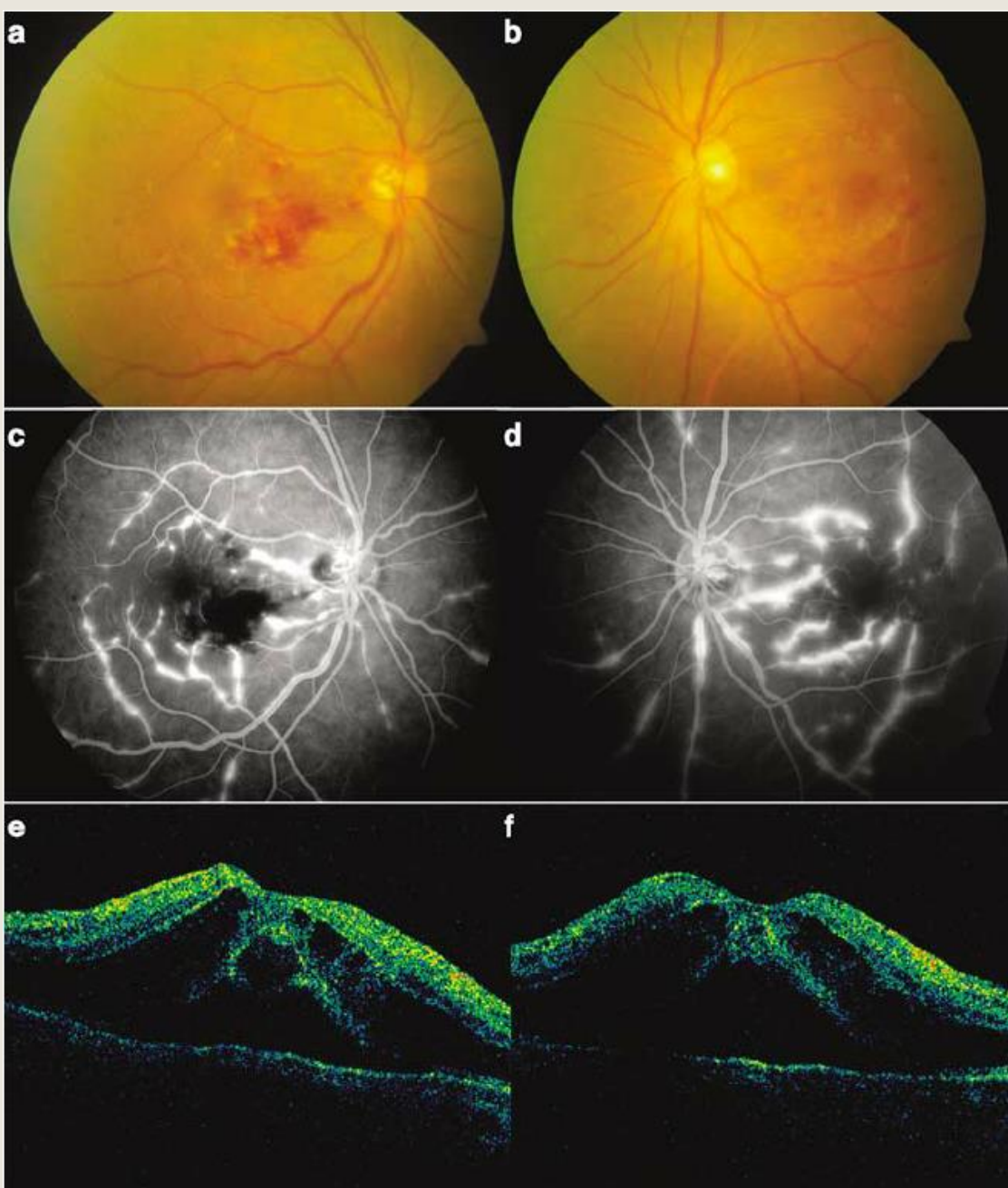


*Uveitis following dengue fever.

Gupta A, Srinivasan R, Setia S, Soundravally R, Pandian DG.
Eye (Lond). 2009 Apr;23(4):873-6. doi: 10.1038/eye.2008.124. Epub 2008 May 9.



CASE STUDY

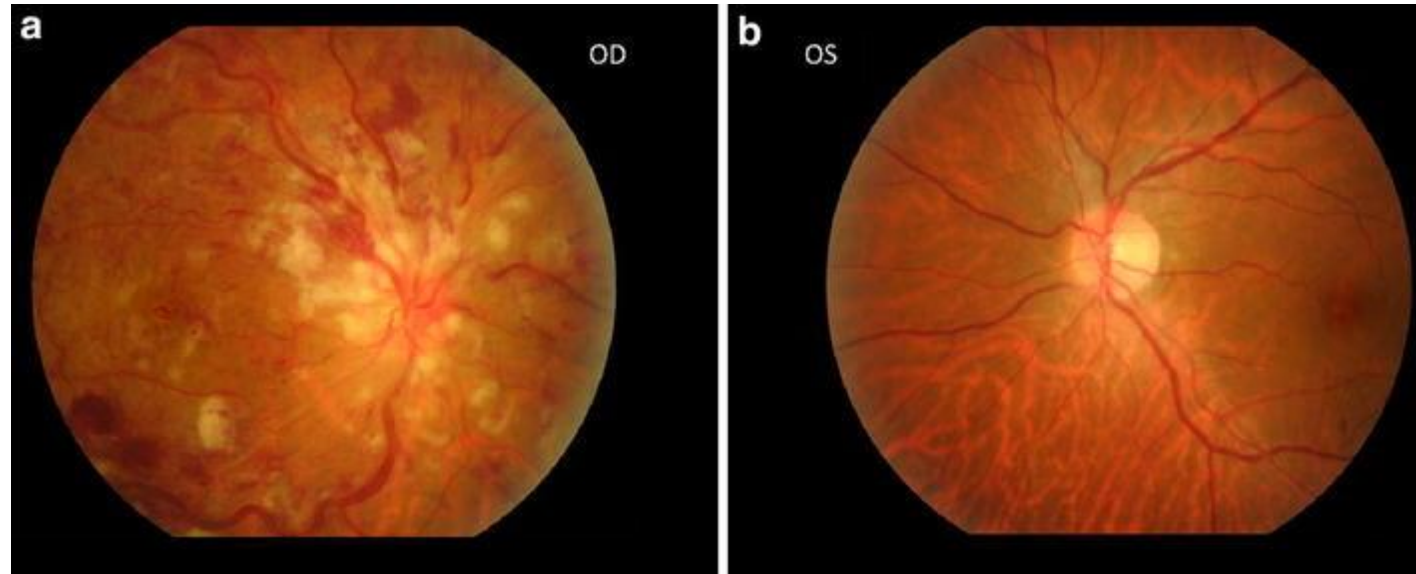


- A 32-year old woman was diagnosed with dengue fever by her GP on day 4 of her febrile illness.
- Blood investigations showed progressive thrombocytopenia and was positive for dengue virus on PCR analysis.
- On day 7 after onset of fever, she noticed sudden painless bilateral blurring of vision upon waking. Platelet count was at its lowest of $26 \times 10^9/L$.
- Visual acuity were 20/400 and counting fingers right and left eyes respectively.
- External and slit lamp examinations were unremarkable and intraocular pressures were within normal limits.
- Dilated fundi examination revealed focal macular chorioretinitis with macular edema associated with vasculitis and flame hemorrhage.
- Fundus fluorescein angiography revealed extensive periphlebitis in both eyes.



OCULAR COMPLICATIONS INVOLVING THE VITREOUS AND RETINA

- Dengue infection can affect the retina microcirculation either by direct viral infection or activation of inflammation through an immune-mediated reaction.
- The pathogenesis of lesions appears to be the same as the clinical disease: haemoconcentration, vasculitis, and coagulation disorders.



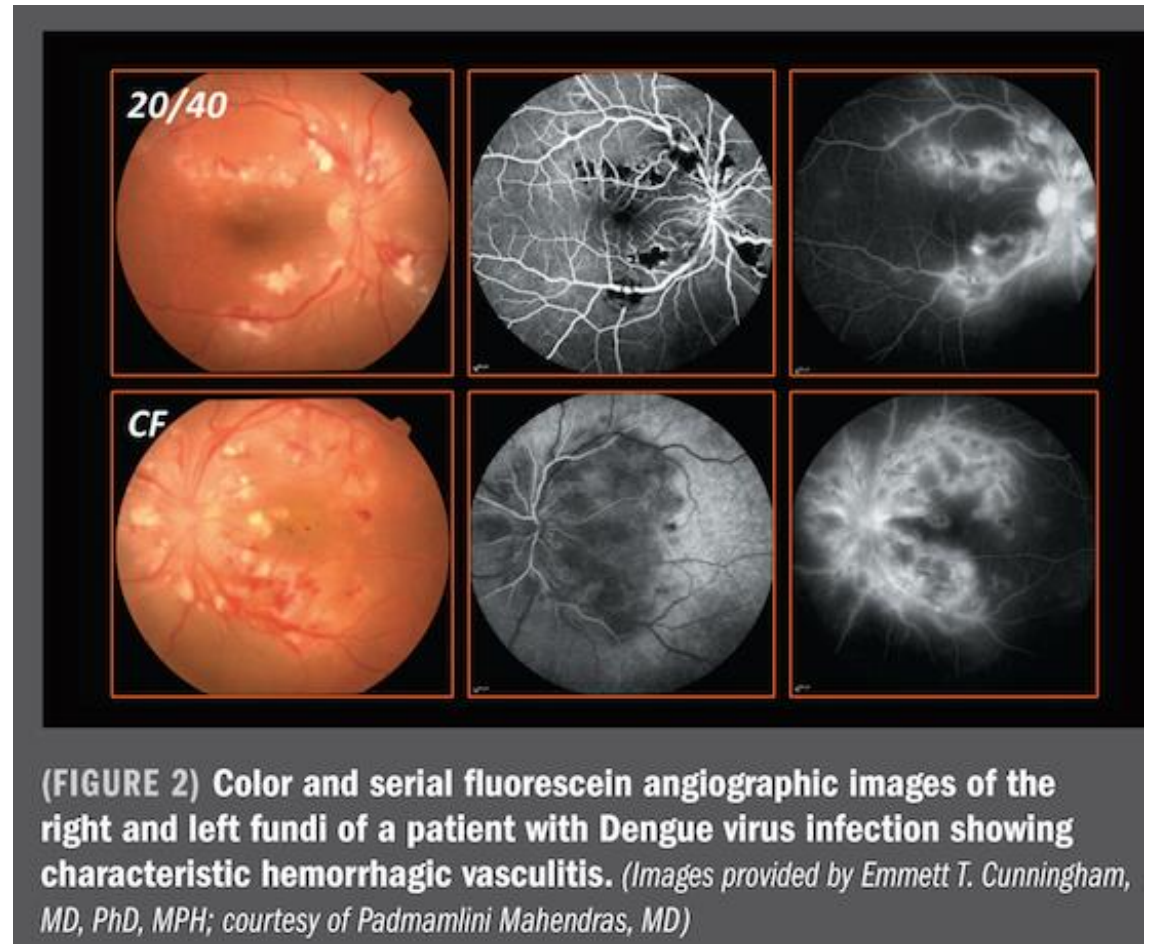
Central retinal vein occlusion concomitant with dengue fever

Punithamalar Velaitham [Email author](#) [View ORCID ID profile](#) and
Nandini Vijayasingham
International Journal of Retina and Vitreous 2016



RETINAL MANIFESTATIONS

- The majority of ocular changes in DFV are in the vascular system of the posterior segment.
- **Maculopathy** is the main retinal manifestation (affecting up to 10% of the cases) and is generally bilateral (73%) and characterized by vasculitis and hemorrhages.*

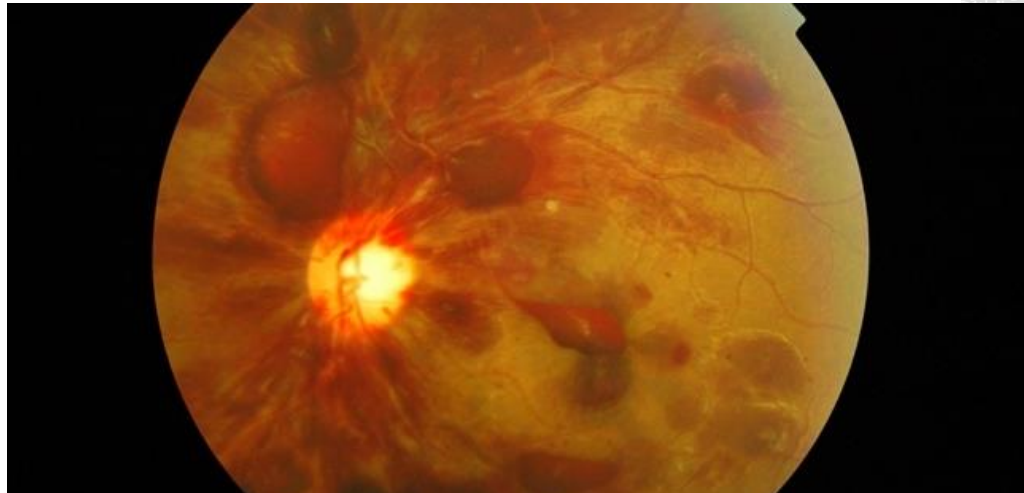


*Arboviruses and the eye

•Gabriel Costa de Andrade [Email author](#), Camila V. Ventura, Paulo Augusto de Arruda Mello Filho, Maurício Maia, Silvana Vianello and Eduardo Büchele Rodrigues



OCULAR COMPLICATIONS INVOLVING THE VITREOUS AND RETINA

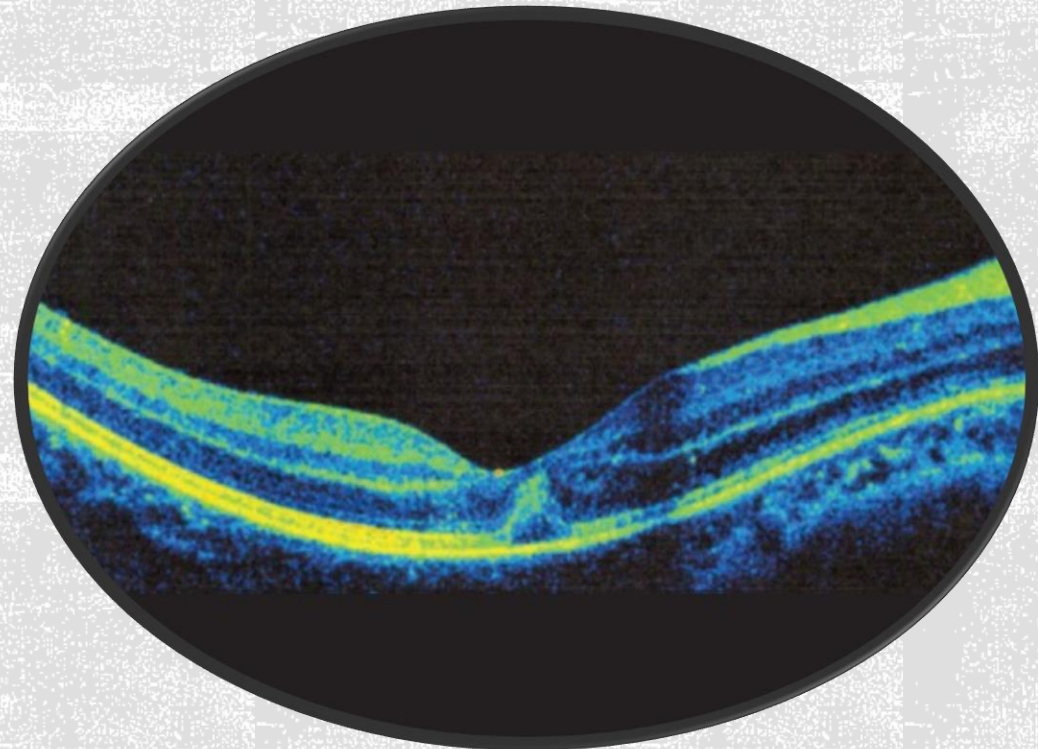
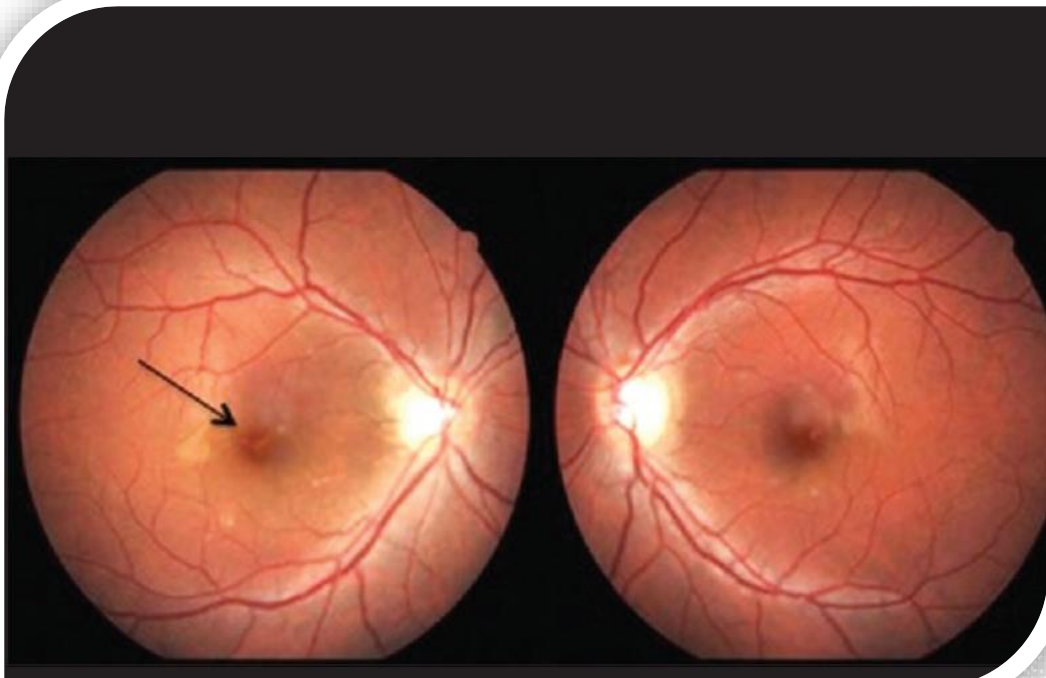


- Haemorrhages associated with dengue-related maculopathy are mostly intraretinal and can take the form of dot, blot, or flame-shaped haemorrhages.
- Vascular sheathing and vasculitis were often found in association with macular haemorrhage.



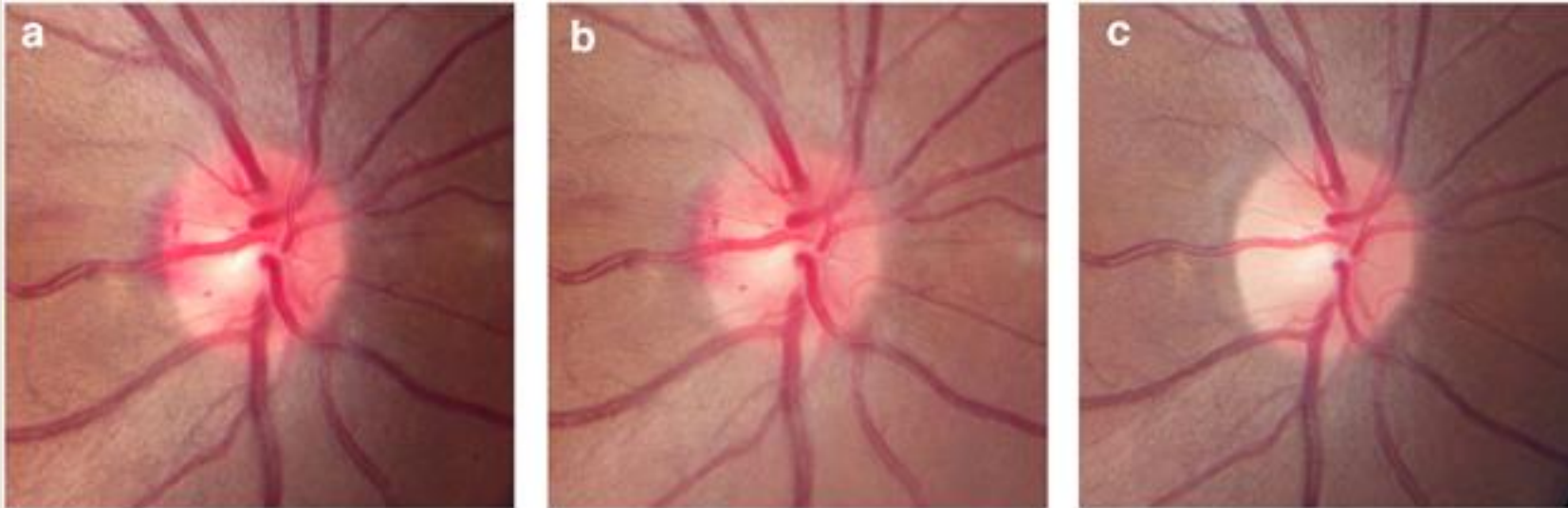
Retinal manifestations

- **Dengue-related foveolitis** refers to the yellow-orange lesion at the fovea of patients with dengue maculopathy, which corresponds to a disruption of the outer neurosensory retina in optical coherence tomography (OCT).
- It was formally described by Loh et al. in 10 eyes of 6 patients and the term **foveolitis** was coined.



■ Optic Neuropathy

- **Optic neuropathy** is relatively **uncommon** compared to other dengue-related ocular signs. This can present with optic disc swelling, hyperaemia, and disc hemorrhages.*



Serial photographs of the right eye in showing the optic disc 1(a), 7(b), and 20(c) days after onset of dengue fever. This case resolved spontaneously with supportive care

Optic neuropathy associated with dengue fever.

Sanjay S¹, Wagle AM, Au Eong KG.



DIFFERENTIAL DIAGNOSIS

- The main differential diagnoses are herpetic and cytomegalovirus retinitis but both of them are more common in immunodeficient individuals with a more exuberant inflammation.
- Although Dengue Retinopathy may morphologically mimic herpetic or cytomegalovirus retinitis, the history of fever, joint pains, and skin rash before the onset of visual symptoms is helpful in the diagnosis, particularly in the endemic regions.



ZIKA

- ZIKV is a mosquito-borne infection, mainly transmitted in Americas by *A. aegypti*, the same vector that transmits DENV and CHIKV.
- Additionally, there are also reports of ZIKV infection following sexual, perinatal and blood transfusion.*
- ZIKV can also lead to severe congenital malformations in newborns whose mothers were infected during pregnancy, especially in the first trimester of pregnancy.



*Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau V, et al. Potential sexual transmission of Zika virus. Emerg Infect Dis. 2015;21(2):359–361. doi: 10.3201/eid2102.141363.



CONGENITAL ZIKA SYNDROME (CZS).

- Although **microcephaly** is the major finding in these newborns, recent publications have described other malformations associated with ZIKV congenital infection including hearing loss, limb anomalies and **ocular findings**.*
- Therefore, a new terminology has been given to this clinical condition, Congenital Zika Syndrome (CZS).

**De Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol. 2016;. doi:[10.1001/jamaophthalmol.2016.0267](https://doi.org/10.1001/jamaophthalmol.2016.0267).*



CONGENITAL ZIKA SYNDROME (CZS).

- A cross-sectional study of forty-three infants with congenital Zika syndrome had severe ocular abnormalities, and all patients had bilateral involvement.
- The data revealed that 12% of cases of congenital Zika with microcephaly had anterior segment abnormalities and 88% had important macular and optic nerve abnormalities.*
- The posterior ocular findings were focal pigment mottling, chorioretinal atrophy with a predilection for the macular area, congenital glaucoma and optic disc abnormalities.
- **Ophthalmic examination is recommended in patients with congenital Zika syndrome.**

*Ventura CV, Maia M, Travassos SB, et al. Risk factors associated with the ophthalmoscopic findings identified in infants with presumed Zika virus congenital infection. *JAMA Ophthalmol.* 2016;134(8):912-918.

*[Cynthia A. Moore, MD, PhD¹](#); [J. Erin Staples, MD, PhD²](#); [William B. Dobyns, MD³](#); et al



RETINAL MANIFESTATIONS

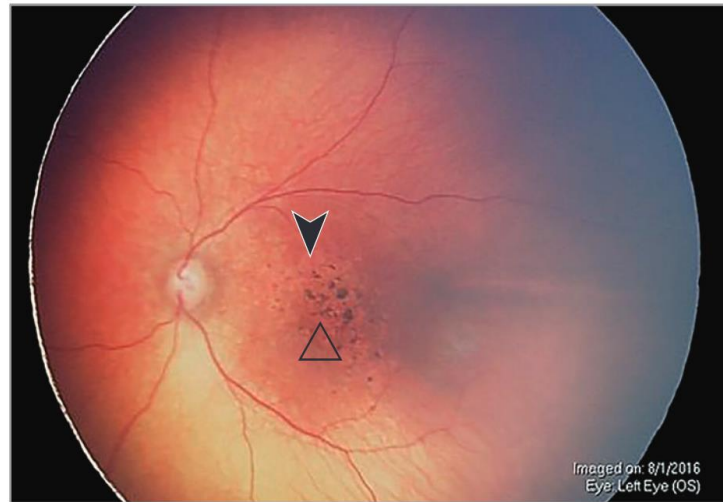
- Ocular abnormalities were detected in infants clinically diagnosed with ZIKV-related microcephaly.
- These findings include gross macular pigment mottling, macular chorioretinal atrophy, optic nerve hypoplasia and increased cup-to-disc ratio.

Figure 2. Severe Pigment Mottling

A Patient A

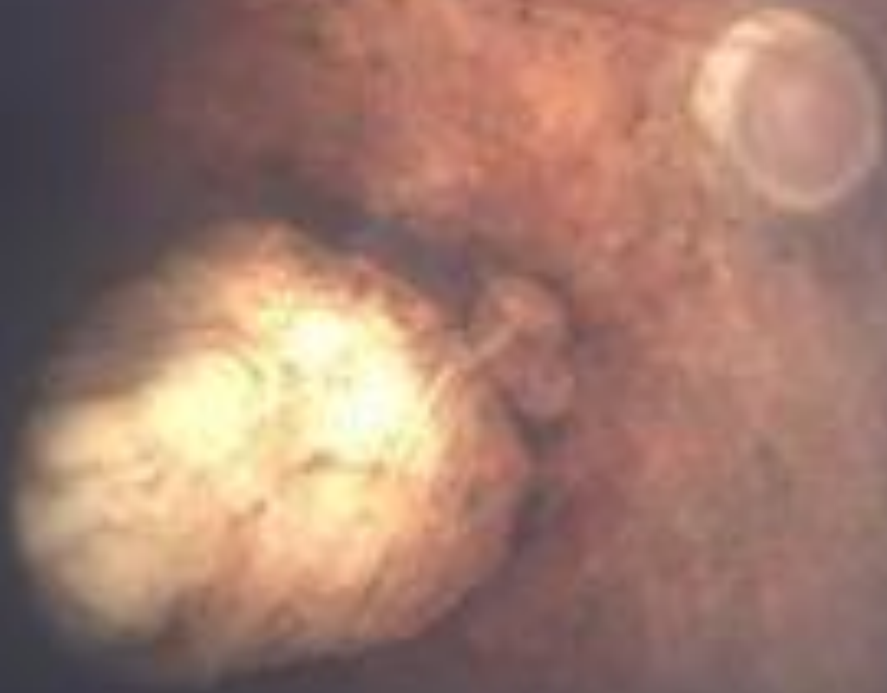


B Patient B



Representative ophthalmoscopy in the left eyes of 2 patients with congenital Zika syndrome demonstrates macular chorioretinal atrophy (open triangles) and focal pigment mottling (arrowheads).

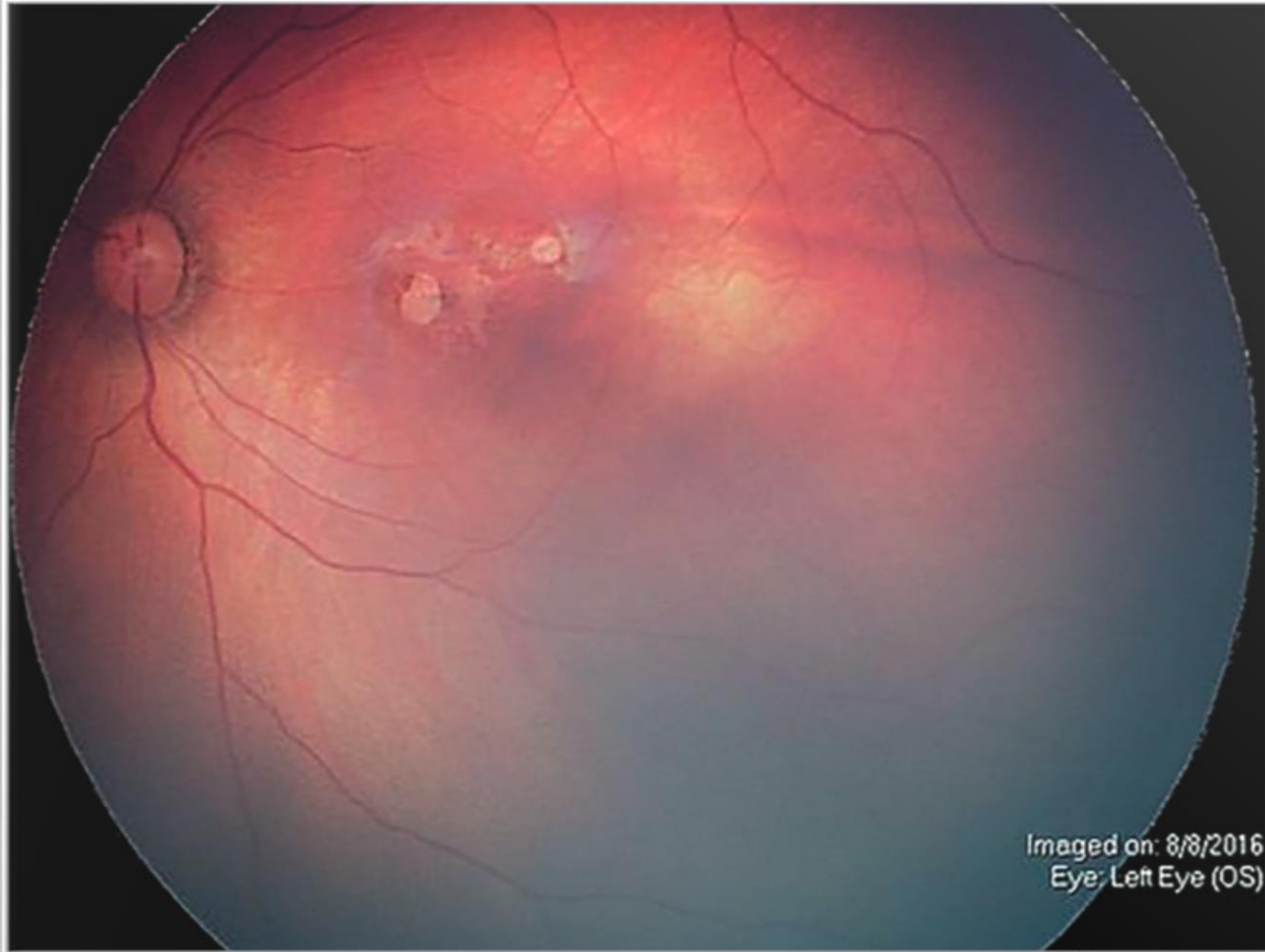




- Wide-angle fundus image (Retcam®) of the right eye of an infant with presumed Zika virus congenital infection showing sharply demarcated chorioretinal scarring with gross pigment mottling on the macula



Figure 3. Chorioretinal Scarring



In particular, retinal lesions, including well-defined chorioretinal atrophy and gross pigmentation, generally affecting the macular region, are unique to ZIKV infection.

Representative ophthalmoscopy in the left eye of a patient with congenital Zika syndrome demonstrates a chorioretinal scar with macular retinal pigment epithelium hypopigmentation and scarce pigment surrounding 2 sharp areas of hypopigmentation (lacunae) with pigmentation in their borders and 250 μm and 500 μm in size.



ZIKA-GENERAL POPULATION

- Only 20% of patients infected with ZIKV are symptomatic. The symptoms include fever, headache, maculopapular rash, arthralgia, and conjunctivitis, which usually lasts for 1 week.
- Recent reports showed a mild disease in adults with acute infection, which can include anterior uveitis and non-purulent conjunctivitis.
- The treatment of anterior uveitis related to ZIKV involves topical corticosteroids and has a benign prognosis.
- Severe disease caused by ZIKV, were recently described in patients from Brazil and French Polynesia, as the Guillain-Barré syndrome and other neurological manifestations in patients infected by the virus.*

*Neurological manifestations of Zika virus infection

[Ana-Belén Blázquez](#) and [Juan-Carlos Saiz](#)



CHIKUNGUNYA



- Chikungunya fever (CHIKV) is an emerging mosquito-borne disease caused by an alphavirus, from the Togaviridae family.
- The vectors are the same species involved in the transmission of DENV and ZIKV.
- CHIKV has been identified in over 60 countries in Asia, Africa, Europe and the Americas. The virus is transmitted from human to human by the bites of infected female mosquitoes.
- After the bite of an infected mosquito, onset of illness occurs usually between 4 and 8 days but can range from 2 to 12 days



SYSTEMIC MANIFESTATIONS

- As with several other mosquito-borne alphaviruses, CHIKV causes a **fever-rash-arthralgia** syndrome in humans.
- The name “Chikungunya” derives from the debilitating joint pain noted by local populations during an outbreak in 1952–1953 in what is now Tanzania.
- The local word means “that which bends up” and the name was given as a result of the stooped posture that resulted from the pain of the disease.



SYSTEMIC MANIFESTATIONS

- Acute infection lasts for 1–10 days and is characterized by an abrupt onset of fever, headache, fatigue, nausea, vomiting, rash, myalgia, and severe arthralgia.
- Joint pains may persist for months to years in some patients
- Diagnosis is made through demonstration of CHIKV IgM antibody in the serum and also by reverse transcriptase-polymerase chain reaction (RT-PCR) from ocular fluids and serum.
- There is no specific antiviral drug treatment for CHIKV; therefore treatment is directed primarily for relieving the symptoms, including the joint pain and fever, using anti-pyretics, optimal analgesics and fluids.



OCULAR MANIFESTATIONS

- Chikungunya virus is known to affect the eye in a myriad of ways ranging from conjunctivitis to retinitis and even optic neuritis.
- Photophobia and retro orbital pain are often seen in the acute phase without any other signs of ocular involvement.
- The main ocular manifestation is an anterior uveitis, often associated with pigmented keratic precipitates and ocular hypertension.
- The management of the anterior uveitis evolves topical and systemic corticosteroids to control inflammation.
- The raised IOP responds well to topical antiglaucoma medications.

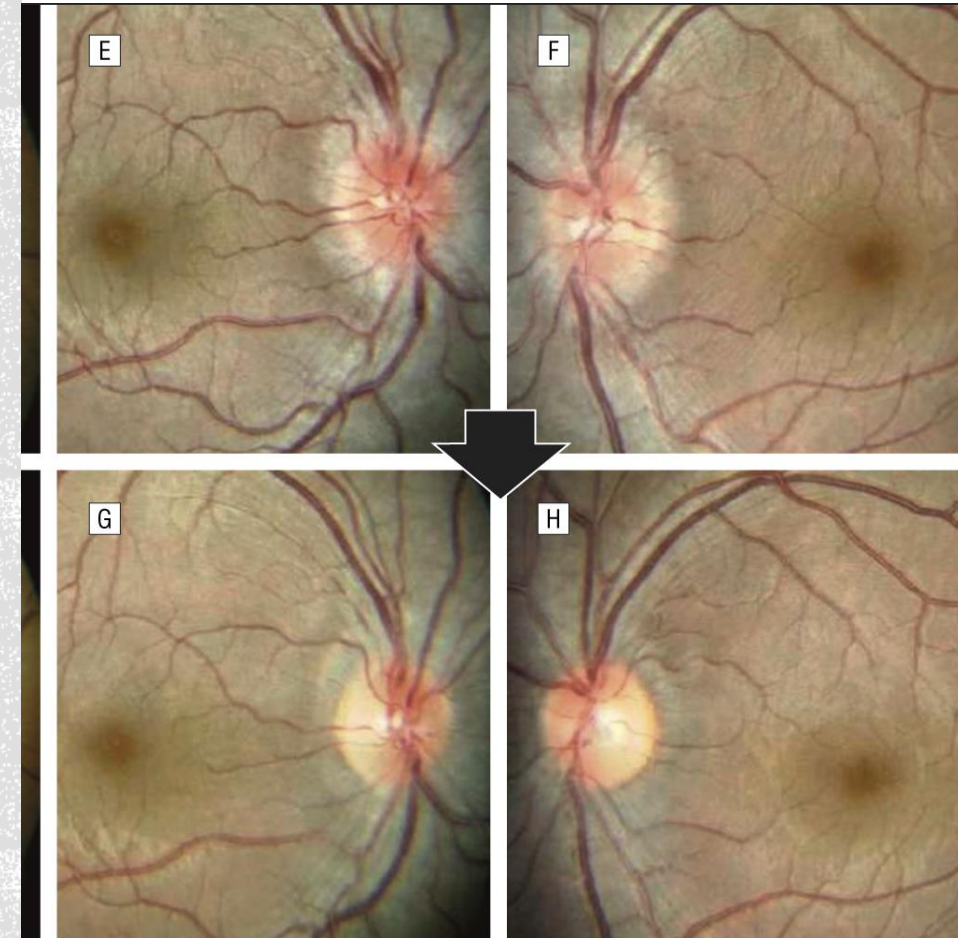


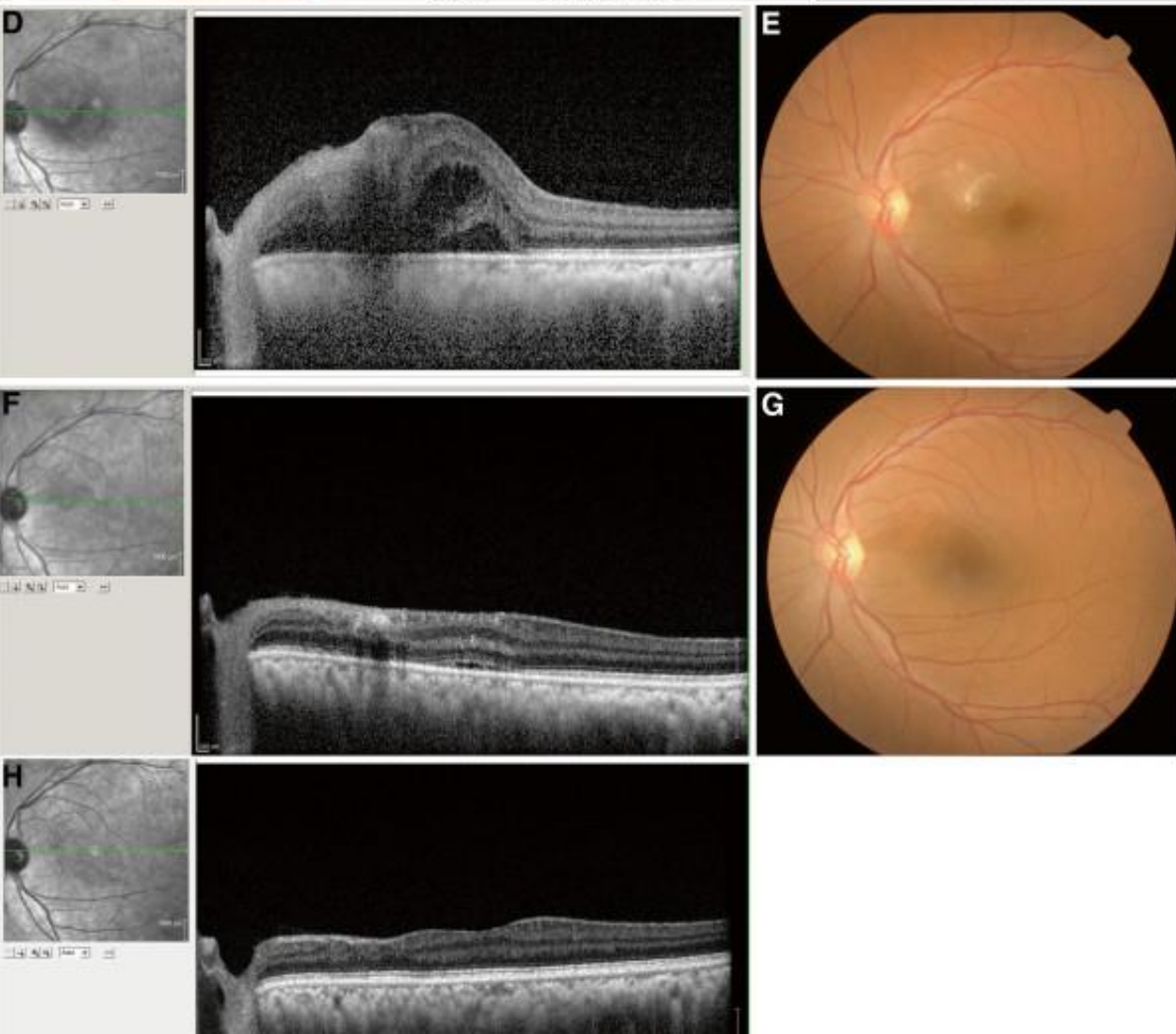
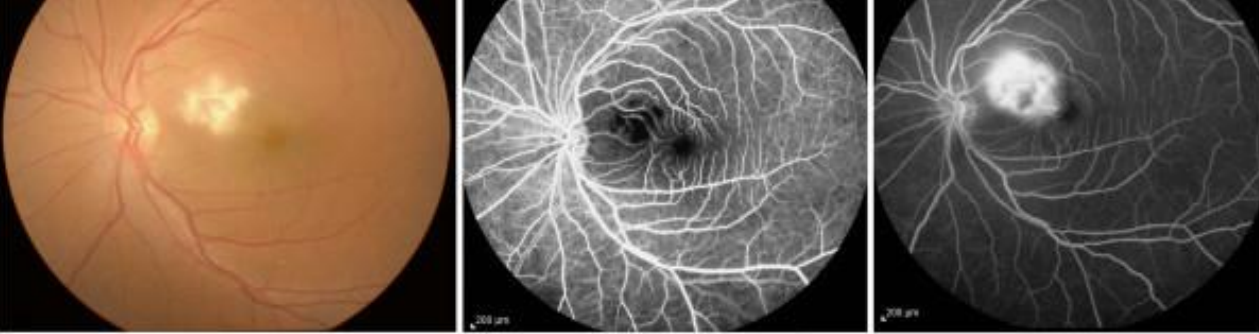
(FIGURE 3) Color photographs of the anterior segment and fundus of a patient with Chikungunya virus infection showing panuveitis and peripapillary retinal vasculitis resembling neuroretinitis. (Images provided by Emmett T. Cunningham, MD, PhD, MPH; courtesy of Rathinam R. Sivakumar, FAMS, PhD)



RETINAL MANIFESTATIONS

- Posterior segment involvement of CHIKV infection may manifest as choroiditis, retinitis, neuroretinitis and optic disc neuritis.
- Chikungunya retinitis (CR) can present at the time of fever or after many weeks or months of the infection.
- Clinical features include vitritis, hyperemic disc, retina hemorrhages, cotton wool spots and multifocal retinitis.





Chikungunya Retinitis

- 45 year old woman complaining of blurred vision 6 weeks following the resolution of chikungunya fever in her left eye.
- Fundus photograph of the left eye showing confluent area of **retinal whitening** suggestive of **retinitis**.
- FFA reveals early hypofluorescence followed by late hyperfluorescence in the posterior pole.
- OCT showed fluid-filled spaces in the outer retina with serous retinal detachment.
- Fundus photograph and OCT showing resolving retinitis lesion 2 weeks after initiation of systemic steroid therapy.
- OCT after 4 months, showing complete resolution of retinitis with thinning of the inner retinal layers nasal to the fovea.



SUMMARY AND CONCLUSION

	Dengue	Zika	Chikungunya
type	flavivirus	flavivirus	alphavirus
Duration of disease	4-7 weeks	1-2 weeks	1-2 weeks
Fever >39	++	+	+++
arthralgia	+++	++	++++
conjunctivitis	+	+++ (20% symptomatic)	+
Retro orbital pain	+++	++	+
Maculopapular exanthema	++	+++	++
uveitis	+	++	+++ with High IOP
retina	Choroiditis, retinitis, macular oedema, neuroretinitis	Macular pigment mottling, macular chorioretinal atrophy, optic nerve hypoplasia	Choroiditis, retinitis, neuroretinitis and optic disc neuritis



THANK YOU.



QUESTIONS

- The Vector for Dengue, Chikungunya and zika is
- A) Anopheles Mosquitoes
- B) Culex mosquito
- C) Aedes aegypti
- D) None of the above
- E) All of the above



QUESTIONS

- Confirmatory tests for dengue infection
- A) IGG and IGM test should be performed in the first 5 days of presentation.
- B) PCR testing should be done late after the fever settles.
- C) Can cross react with testing for chikungunya.
- D) PCR testing is best done early during the febrile phase



QUESTIONS

- Arboviruses cause the following diseases except:
 - A) Encephalitis
 - B) Febrile diseases
 - C) Haemorrhagic fevers
 - D) Pneumonia



QUESTIONS

- What are symptoms of Zika infection
- A) Headache, fever, rash
- B) Red eyes (conjunctivitis)
- C) Musclepain, joint pain, and weakness
- D) All of the above



QUESTIONS

- Which of these conditions is least likely to present with conjunctivitis
- A) Dengue
- B) Zika
- C) Chikungunya



QUESTIONS

- What should I do with a patient who is sero-positive for arbovirus infection and is complaining of blurred vision, blind spots and/or floaters?
- A) Observe for a few weeks to see if the condition improves
- B) Give antibiotic drops and lubricants
- C) Refer to an Ophthalmologist for a complete eye exam

