ZICA Outbreak Control and Prevention State Cell
Health & Family Welfare Department
Government of Kerala

NO: 1/F2/483/2021-HEALTH- Dated 9th October 2021

In superseding all the previous advisories, guidelines regarding the patient management and treatment for the Zica virus outbreak, the revised updated Guidelines is issued for practicing in the State of Kerala.

The Guidelines are attached as an Annexure. The Guidelines shall be followed up by the treating teams and the Hospital Medical Board. If there are any doubts, the treating teams may consult the State Medical Board.

PRINCIPAL SECRETARY

GUIDELINES FOR PREVENTION AND CONTROL OF ZIKA VIRUS DISEASE IN KERALA

Version 1

9th October 2021

Department of Health & Family Welfare
Govt. of Kerala

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Introduction

Zika virus disease is an emerging arboviral disease caused by the single-stranded RNA virus called Zika virus, which belongs to the family Flaviviridae. It is transmitted by Aedes mosquitoes like A. *aegypti* and A. *albopictus.* It was first identified in Uganda in 1947. Human cases were first reported from Uganda and Tanzania in 1952, and since then, outbreaks of Zika virus disease have been recorded in Africa, the Americas, Asia, and the Pacific, including several parts of India. World Health Organization has declared Zika virus disease as a Public Health Emergency of International Concern (PHEIC) on 1 February 2016. The first case of Zika viral disease in India was reported in Gujarat in 2016.

A majority of those infected with Zika virus disease either remain asymptomatic (up to 80%) or show mild symptoms of fever, rash, non-purulent conjunctivitis, myalgia, and arthralgia. Zika virus infection should be suspected in patients reporting an acute onset of fever, maculopapular rash, non-purulent conjunctivitis, and arthralgia, among those who reside in areas with ongoing Zika transmission or those who have travelled to areas with ongoing transmission during the two weeks preceding the onset of illness. Zika virus has also been associated with microcephaly in the newborn and other related adverse pregnancy outcomes, including miscarriages, stillbirth, eye defects, hearing deficits, limb abnormalities, and impaired growth. Neuroinflammatory syndromes like Guillain Barre Syndrome, acute disseminated encephalomyelitis [ADEM], and transverse myelitis have also been found temporally associated with Zika virus infection, as evident in reports from French Polynesia and South America. On 8 July 2021, Zika virus disease was first reported in Kerala state from Thiruvananthapuram district.

Transmission of Zika virus

Transmission dynamics of the Zika virus is usually through either vector-borne mode or non-vector borne route.

ZIKV vector-borne transmission

Members of the Aedes family like *Aedes aegypti, Aedes polynesiensis, Aedes Albopictus, Aedes vittatus* are the potential vectors responsible for the transmission of ZIKV infection. Vector-borne transmission through the bite of infected Aedes mosquitoes is the major route of transmission of ZIKV.

Non-Vector Borne Transmission of ZIKV

Zika virus RNA has been detected in blood, urine, semen, saliva, female genital tract secretions, cerebrospinal fluid, amniotic fluid, and breast milk

1. **Maternal-foetal transmission [during antenatal period or peripartum]**
2. **Unprotected sex, including vaginal, anal, and oral sex**
    - Semen – Zika virus RNA can be detected in semen even when it is no longer detectable in blood. Zika virus RNA usually clears from semen after about three months but has been detected in semen up to 188 days after onset of illness.
    - Sexual transmission of the Zika virus as late as 41 days after a partner's onset of symptoms has been described. Infectious Zika virus in semen (detected via culture) has been detected as late as 69 days after onset of illness.
    - Zika virus RNA has been detected in female genital tract secretions (via endocervical swabs and cervical mucus) during symptomatic illness. Zika virus RNA has also been detected in cervical mucus 14 days after onset of illness when it was no longer detectable in blood or urine.
    - Men (whether symptomatic or not) should wait at least three months after symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic) before unprotected sex.
    - Women (whether symptomatic or not) should wait at least eight weeks after symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic) before unprotected sex
3. **Transfusion of infected blood products**
    - Blood – In nonpregnant individuals with Zika virus infection, Zika virus RNA is usually detectable in the serum for about two weeks and in whole blood as late as 81 days.
    - In pregnancy, Zika virus RNA has been detected in the serum as late as 107 days.

4. **Organ transplantation**
5. **Laboratory exposure**
6. **Others**
    - **Urine** – Zika virus RNA usually clears from urine after about six weeks. Zika virus RNA has been detected in urine up to 91 days after onset of illness.
    - **Saliva** – Zika virus RNA has been detected in saliva up to 91 days after onset of illness. The replicating virus has been detected in saliva at the time of symptomatic illness.
    - **Tears** – Zika virus RNA has been detected in tears up to 30 days after onset of illness

Clinical manifestations

- The incubation period between mosquito bite and onset of clinical manifestations is typically 2 to 14 days. The illness is usually mild; symptoms resolve within two to seven days. Immunity to reinfection occurs following primary infection. Severe disease requiring hospitalization is uncommon, and case-fatality rates are low.

Symptoms and signs

- Clinical manifestations occur only in 20 to 25 per cent of individuals who become infected with the Zika virus. Symptoms and signs of Zika virus infection typically include
    i. Acute onset of low-grade fever (37.8 to 38.5°C)
    ii. Pruritic rash (erythematous macules and papules may be present on the face, trunk, extremities, palms, and soles)
    iii. Arthralgia (notably in the small joints of the hands and feet) and conjunctivitis (non-purulent).
- Other commonly reported clinical manifestations include myalgia, headache, dysesthesia, retro-orbital pain, and asthenia. Less commonly observed symptoms and signs include abdominal pain, nausea, diarrhoea, bilateral lower limb oedema and mucous membrane ulcerations. Severe myalgia, myositis and rhabdomyolysis have also been observed rarely in Zika during viremia or later as autoimmune myositis triggered by Zika. Immune-mediated thrombocytopenia has been observed. Other manifestations like facial puffiness, palatal petechiae, uveitis, transient hearing

impairment, Myocarditis, and pericarditis have been reported rarely. ZIKV among organ transplant recipients may present with graft dysfunction and thrombocytopenia.

Complications

- Complications due to ZIKV in immunocompetent persons is infrequent. Complications include Myocarditis, pericarditis, uveitis, immune thrombocytopenia, and transient hearing loss. Myositis with rhabdomyolysis has also been observed rarely. In organ transplant recipients, graft dysfunction and thrombocytopenia can occur. Intrauterine and neonatal complications due to ZIKV are discussed separately.
- ZIKV has been associated with many neurological complications like
    i. Guillain Barre syndrome.
    ii. Encephalitis
    iii. Transverse myelitis
    iv. Encephalomyelitis
    v. Meningoencephalitis
    vi. Chronic inflammatory demyelinating polyneuropathy
    vii. Neuropsychiatric and cognitive symptoms

Case definition:

Suspect case:

Patient with skin rash or elevation of body temperature ≥ 37.2 degrees Celsius with at least of the following symptoms (not explained by other medical conditions):

i. Arthralgia or myalgia
ii. Non-purulent conjunctivitis or conjunctival hyperaemia
iii. Headache or malaise
iv. With a history of travel to countries/areas with the indigenous transmission of Zika Virus Disease in the last two weeks or living in an area with ongoing transmission.
v. Guillain-Barre syndrome not known to be associated with any other aetiology.
vi. A complication of pregnancy (foetal loss in a mother with compatible illness and/or epidemiologic risk factors; or in utero findings of microcephaly and/or intracranial calcifications with maternal risk factors)

Confirmed case:

- A suspected case with positive laboratory results for the specific detection of Zika Virus by RT-PCR

Epidemiological linkage

Epidemiological linkage is defined as

- Travel to a country or region/or living in a region with known Zika virus transmission, or
- Unprotected sexual contact with a laboratory-confirmed case of Zika virus infection, or
- Receipt of blood or blood products within 30 days of symptom onset; or
- Organ transplant recipient within 30 days of symptom onset; or
- Association in time and place with a confirmed or probable cause.

Local transmission

Local transmission can be defined as a lab-confirmed case of Zika virus disease who:

- Who has not travelled to an area reporting confirmed cases of Zika virus disease, or
- Had no sexual exposure to a person travelling from Zika affected area or other known exposure to body fluids of an infected person.
- There could be single or multiple foci of local transmission. There may or may not be an epidemiological link to a travel-related case.

Differential diagnosis

- ZIKV must be differentiated from other exanthematous fevers and tropical fever syndromes, including COVID-19. In areas endemic for Dengue Fever, Chikungunya, and Zika, co-infection is likely to occur rarely.

Differential Diagnosis	Clinical features	Differentiating feature from Zika
Dengue fever	High-grade fever, severe muscle pain, rash, and headache. It may also be associated with haemorrhage	Conjunctivitis is rare in dengue. Fever not high grade in Zika. Haemorrhage not seen in Zika.

Differential Diagnosis	Clinical features	Differentiating feature from Zika
Chikungunya	High-grade fever, intense joint pain affecting the hands, feet, knees, and back, pruritic rash	Conjunctivitis is rare in chikungunya. Fever is not high grade in Zika.
Rubella	Low-grade fever, Macular rash, coryza, arthritis, lymphadenopathy	Conjunctivitis is rare in Rubella, and coryza is rare in Zika.
Measles	High-grade fever, cough, conjunctivitis, lymphadenitis. and morbilliform rash.	Fever low grade in Zika. Coryza is rare in Zika. Rash in measles from day 4, rash in Zika from day 1.
Leptospirosis	High-grade fever, rigors, myalgia, conjunctival suffusion, headache, arthralgia	Fever low grade in Zika and jaundice is absent. Rash is rare in leptospirosis.
Malaria	Periodic high-grade fever, malaise, nausea, vomiting, abdominal pain, diarrhoea, myalgia	Rash, lymphadenopathy, and conjunctivitis is usually not seen in malaria.
Scrub typhus	High-grade fever, headache, eschar, lymphadenopathy, and rash	Eschar not seen in Zika. Conjunctivitis is rare in scrub typhus.
COVID-19	Fever, headache, rash, sore throat, conjunctivitis, rash	Coryza not common in Zika.
Parvovirus	Acute symmetric arthritis or arthralgia	A rash may or may not be present in parvovirus infection

Comparison of symptoms for Dengue Fever, Chikungunya and Zika

Symptoms	Dengue	Chikungunya	Zika
Fever	++++	+++	+++
Myalgia/Arthralgia	+++	++++	++
Oedema of extremities	0	0	++
Maculopapular rash	++	++	+++
Retro-orbital pain	++	+	++
Conjunctivitis	0	+	+++

Lymphadenopathies	++	++	+
Hepatomegaly	0	+++	0
Leukopenia/Thrombopenia	+++	+++	0
Haemorrhage	+	0	0
Adapted from Halstead et al. and Yap State Department of Health Services presentation			

Laboratory diagnosis

- The diagnosis of Zika virus infection should be suspected in individuals with typical clinical manifestations and relevant epidemiologic exposure. The diagnosis of Zika virus infection is definitively established via Real-Time Reverse-Transcription Polymerase Chain Reaction (rRT-PCR) for Zika virus RNA (in serum or urine) or Zika virus serology [Zika IgM followed by Plaque Reduction Neutralization Test (PRNT] if IgM positive]. Serum and urine are the primary diagnostic specimens.
- **RTPCR-TRIOPLEX OR MONOPLEX PCR**: Trioplex PCR can simultaneously identify Zika, Dengue, and Chikungunya RNA, whereas monoplex PCR can identify only ZIKV RNA.
- Trioplex PCR can be performed on serum, urine, plasma, CSF, and amniotic fluid.
- In persons symptomatic for less than seven days - Serum PCR should be done.
- In persons symptomatic for more than seven days and less than 20 days –Urine PCR should be done.
- In persons with myositis with rhabdomyolysis without an alternative diagnosis - send serum and Urine samples for Zika PCR. If PCR is negative, Zika IgM and PRNT should be done [sample to be sent to NIV, Alappuzha]
- In the case of neuroinflammatory syndromes - Serum/Urine PCR. If PCR is negative, serum is to be sent for Zika IgM. If Zika IgM is positive, a plaque reduction neutralization test [PRNT] should be performed.

Clinical management

- ZIKV is self-limiting. There is no specific treatment for Zika virus infection. Management consists of rest and symptomatic treatment.Management neuroinflammatory syndromes are discussed separately.

Zika virus neurological aspects

- Zika virus is a Flavivirus spread by the Aedes aegypti mosquito that shows neurotropism resulting in congenital microcephaly, Guillain-Barré syndrome, myelitis, and meningoencephalitis. Compared to Chikungunya, Zika more often affects the peripheral nervous system more than the central nervous system. The most typical neurological manifestation of Zika virus infection is the Guillain Barre syndrome (GBS), followed by encephalitis and myelitis. Rare manifestations were facial paralysis, meningitis, meningoencephalitis, and optic neuritis. Dual infection with Zika and Chikungunya was associated with stroke. Death was reported in less than 10% of patients.

Guillain Barre syndrome (GBS)

- GBS patients present with pain, paraesthesia or numbness of extremities followed by progressive weakness of limbs with areflexia. Since patients presenting with ascending quadriparesis has a broad differential diagnosis, they should be promptly referred to a specialist with facilities for intensive care to manage these patients. Muscle power is monitored using Medical Research Council (MRC) sums score that evaluates global muscle strength. Manual strength of six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion) is evaluated on both sides using the MRC scale. The summation of scores gives MRC-sum score, ranging from 0 to 60. They must be admitted and observed in an intensive care unit to monitor for respiratory failure and autonomic disturbance (hypotension, hypertension, and cardiac arrhythmias. To identify patients at risk of respiratory failure, we can use the '20/30/40 rule'; vital capacity is <20ml/kg, the maximum inspiratory pressure is $<30cmH_2O$, or the maximum expiratory pressure is $<40cmH_2O$. The autonomic function must be monitored using ECG and blood pressure. Identification of GBS can be difficult, with an atypical presentation like facial paralysis or bulbar weakness with paraesthesia or GBS variants like Miller Fischer syndrome (extraocular muscle paralysis, ataxia and areflexia).
- In GBS, nerve conduction study most often shows a demyelinating pattern, less often axonal. Serum potassium and magnesium will be normal. CSF analysis can show albumin-cytological dissociation.

- Rapid immune modulation with intravenous immunoglobulin (0.4 g/kg daily for 5 days) and therapeutic plasmapheresis (200–250 ml/kg for 5 sessions) have been proven to reduce the mortality and morbidity of patients with GBS. We offer therapeutic plasmapheresis for haemodynamically stable patients and intravenous immunoglobulin for haemodynamically unstable patients. They also require limb and chest physiotherapy. Medical Complications include deep vein thrombosis due to immobilization, ventilator-associated pneumonia, and hyponatremia. No specific anti-glycolipid antibody has been associated with GBS associated with ZIKV infection. We must promptly detect complications like cardiac arrhythmias, infections, deep vein thrombosis, pain, delirium, depression, urinary tract infection, constipation, corneal ulceration, hyponatremia, and pressure sores.
- We need to initiate an early rehabilitation programme. Also, manage long-term complaints like fatigue, pain, and psychological distress.

Acute disseminated encephalomyelitis (ADEM), Myelitis&Encephalitis.

- Inflammatory disease can affect the brain and or spinal cord as a post-infective or Para infectious disease. Brain affection can present with sub-acute onset ataxia, altered sensorium, brainstem symptoms or language dysfunction. Lesions in the spinal cord lead to paraparesis or quadriparesis with urine retention, to begin with, and later incontinence. Patients can have restricted forms in the form of encephalopathy, or spinal cord syndrome, optic neuritis, or can present in combination.
- The brain lesions are seen as ill-defined blotchy lesions affecting grey and white matter on MRI. Spine MRI may show longitudinally extensive transverse myelitis (LETM), and orbital MRI is done to look for the extend of optic nerve involvement. Serum NMO and MOG antibody, and CSF analysis including oligoclonal band should be examined.
- Treatment is often initiated with IV Methylprednisolone (IVMP) 1 gram once daily for 3-5 days. If the patient does not respond to IVMP, plasma exchange (200–250 ml/kg for 5 sessions) is initiated in hemodynamically stable patients. Intravenous immunoglobulin (0.4 g/kg daily for 5 days) can be given in patients who do not respond to therapeutic plasma exchange.

Zika virus and pregnancy

- There is no evidence that pregnant women are more vulnerable to acquiring Zika virus infection or that this infection causes a more serious illness in pregnant women. WHO concluded -Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly. Maternal ZIKA infection tends to have more adverse effects on the foetus than on the mother, as maternal symptoms are usually self-limiting. Maternal infection can lead to foetal infection where it kills neuronal progenitor cells and disrupts neuronal proliferation, migration, and differentiation there by slowing brain growth in the foetal brain. Foetus infected in early gestation is more likely to be affected compared to infection later in pregnancy.

Cranial abnormalities	Extra-cranial abnormalities
Microcephaly	Foetal growth restriction
Cerebral calcifications	Oligohydramnios
Ventriculomegaly	Talipes
Cortical and white matter abnormalities 9eg. Agyria, pachygyria, lissencephaly)	Muscle contractures/ arthrogryposis
Periventricular cysts	Cardiac abnormalities
Callosal abnormalities	Diaphragmatic Hernia
Cerebral and Cerebellar atrophy (transverse diameter <5th percentile)	
Posterior fossa abnormalities 9vermian agenesis, Blake's cyst, Mega Cisterna Magna (>95th percentile)	Adverse Pregnancy Outcomes (1-4%)
Brain stem / spinal cord degeneration	Miscarriage
Ocular abnormalities (intraocular calcifications, cataracts, microphthalmia, macular alterations, optic nerve abnormalities)	Pre-term birth Stillbirth

Transmission

- Aedes aegypti mosquitoes - primary vector for transmission Sexual transmission rare

- Virus has been shown to be present in semen (69 days), vaginal secretions and menstrual blood.
- Zika virus can be transmitted by blood transfusion

Clinical presentation

- Incubation period - 3 to 12 days (Max 14 days) 80% asymptomatic and 20% symptomatic.
- Symptoms include Fever (mild) / Maculopapular rash / itching / pruritus / Headache / Arthralgia/ arthritis / Myalgia / Conjunctivitis / Retro-orbital pain.

Screening and surveillance

- All pregnant women should be asked for:
- History of fever with rash in the past 12 weeks
- History of close household contact with a ZIKA positive patient
- Travel or residence (3km radius) to an area with ongoing Zika virus transmission before or during current pregnancy
- Possible sexual exposure before or during pregnancy (partner had ZIKA virus infection/ travel to an area with ongoing ZIKA infection.)

Evaluation and follow up of a Zika virus infection

Pregnant women presenting with fever, rashes, arthralgia, conjunctivitis, myalgia, headache, and malaise

Blood testing - NAAT RTPCR for Zika Virus, along with testing for dengue and Chikungunya

If positive for ZIKA Virus

1. Home isolation
2. Baseline Ultrasound
3. 4-weekly follow up scan
4. Counselling-regarding possible adverse effects (miscarriage, anomalies, preterm birth, and stillbirth).
   - Offer option of termination in first trimester as 5-10 % risk of congenital anomalies.
   - In second trimester do baseline ultrasound and repeat sonogram in four weeks or earlier (MRI in indicated cases as per radiology opinion) decision for termination on an individual basis depending on foetal affection

Pregnant women with history of fever and rash in the past 12 weeks

TEST – ZIKA VIRUS Antibody and ZIKA virus PRNT Rpt

Antibody after 2wks to note increase in titre

If negative routine antenatal care.

III Asymptomatic pregnant women with ongoing possible Zika virus exposure

Zika virus NAAT RTPCR during each trimester

- Positive

Acute Zika virus infection

- Negative

No ZIKA virus RNA detected (ZIKA virus infection cannot be ruled out)

IV Asymptomatic pregnant women with recent possible exposure but withoutongoing possible exposure - Testing not routinely recommended.

Test for TORCH and Zika virus.

Further evaluation and management decision by multidisciplinary team including foetal medicine specialist.

V Antenatal women presenting with USG showing microcephaly

Role of Amniocentesis:

- Usefulness of Amniocentesis is unknown
- A negative amniotic fluid best result cannot rule out congenital Zika virus infection.
- The result of serial amniocentesis tests has demonstrated that Zika virus RNA may be present only transiently.
- Even if positive, it is not known how sensitive this test is for congenital infections,

nor the likely hood of an infected foetus being affected.

- Amniocentesis may be considered in a patient reporting with microcephaly in consultation with a foetal medicine specialist.

Other specimen to be sent for testing

- In case of abortion / still birth - cord blood / placenta bit and membrane for microbiological examination.
- Foetus and placenta for histopathological examination.

Treatment

- Symptomatic treatment
- Paracetamol for fever and pain
- Antihistamines for itching
- Rest
- Adequate fluids
- Aspirin and other NSAID should be avoided until dengue can be ruled out to reduce the risk of haemorrhage.
- Features of Guillain Barre Syndrome require urgent assessment and specialist management.

Prevention

- Currently no vaccine or drug is available.
- Prevention relies on reducing mosquitoes through source reduction and reducing contact between mosquitoes and people
- Light-coloured, loose-fitting clothes that cover as much exposed skin
- Repellents - 50% N, N-diethyl meta toluamide (DEET) [DEET up to 50% concentration is safe in pregnancy]
- Permethrin impregnated mosquito net

- Physical barriers such as window screens, closed doors, and windows
- Mosquito breeding sites should be cleaned or removed
- Pregnant women should consider postponing non-essential travel until after the pregnancy.

Annexure(I) Clinical guideline for couples undergoing ART duringZika virus outbreak

Annexure (II) Guidelines for antenatal USG during Zika virus outbreak

Annexure (I)

Clinical guidelines for couples undergoing Assisted Reproductive Technologies during ZIKA Virus outbreak

- Men who have confirmed Zika virus disease should wait for at least three months after onset of illness to attempt reproduction. For women with confirmed infection should wait for at least 8 weeks after the onset of illness to attempt pregnancy.
- Couples at the risk of Zika disease undergoing ART: Asymptomatic men and woman who are at risk of Zika virus, deciding to undergo ART should be offered testing (NAT) at the start of stimulation. to avoid proceeding with a NAT positive patient.
- A repeat testing is offered close to ovum pick up in a fresh cycle or embryo transfer in case of frozen embryo cycle.
- For males and females with positive NAT, the gametes / embryo is cryopreserved and quarantined for 3 months from the time of the last positive result.
- Sperm donation in men with Zika virus disease: Men with Zika infection are considered ineligible for a period of 6 months from the onset of illness.

Antenatal ultrasound guidelines for Zika viral disease

Algorithm for follow up of suspected/proven antenatal neonates:

- Timing: First day of life – Neurosonogram
- If not resolved by Neurosonogram – MRI Brain

- CT Brain for confirmation of calcification.

Timing and frequency of antenatal USS:

- Literature says duration from exposure to Zika Virus to the development of findings on foetal ultrasound is highly variable – it can be as short as two weeks and as long asup to late in third trimester.
- Pregnant ladies for antenatal ultrasound can be categorized into three as follows for defining the timing and frequency of antenatal ultrasound.
- Category – 1 (Zika suspect – antenatal patients in any trimester from endemic or area with local transmission, history of possible exposure to Zika virus, travel to the endemic area / symptomatic or asymptomatic / lab negative
- USS examination as recommended for routine antenatal care. But closer monitoring needed in selected cases as directed by Obstetrician.
- Category – 2 (Zika Positive – antenatal patients from any area, in any trimester):
- Immediate ultrasound scanning required.
- Findings of congenital Zika virus syndrome, if present, clinical management according to guidelines is suggested.
- Ultrasound reveals no findings suggestive of congenital Zika virus syndrome, there is no consensus on how to follow up by ultrasound. Reasonable recommendation is serial ultrasound every four weeks till delivery. One ultrasound is mandatory between 25 to 33 weeks.
- Category – 3 (Antenatal patients from any area, any trimester, asymptomatic and lab positive): This category comes when mass level screening starts.
- Immediate ultrasound scanning required.
- Findings of congenital Zika virus syndrome, if present, clinical management according to guidelines is suggested.
- Ultrasound reveals no findings suggestive of congenital Zika virus syndrome, there

is no consensus on how to follow up by ultrasound. Reasonable recommendation is serial ultrasound every four weeks till delivery. One ultrasound is mandatory between 25 to 33 weeks.

Common findings to look for:

- First trimester – 11 to 13 weeks - abnormal Nuchal Translucency/Nasal B/gross CNS anomalies
- Second trimester –Routine biometry to detect microcephaly.

Definition for microcephaly:

- WHO definition: Head circumference>2 standard deviations (SD) belowthe mean or <3rd percentile for gestational age (standard growth charts for sex, age, and GA at birth)
- Society For Maternal Foetal Medicine: ≥3 SD below the mean for gestational age, >5 SD below the mean for gestational age (diagnostic)
- If the head circumference is between 3rd and 5th SD – Detailed Neurosonogram and MRI if needed.

Measuring head circumference on ultrasound:

- Axial image of foetal head at the level of paired thalami, 3rd ventricle and cavum septum pellucidum. The structures on both sides of the falx should be symmetrical. The entire head is seen from frontal bone to occipital bone. By using elliptical callipers, outline the outer edge of the skull.
- IC calcifications – involving Gray matter - White matter junction or Basal Ganglia and Thalami
- Other findings:
    - Head shape irregular
    - Ventriculomegaly
    - Cystic lesions
    - Intraventricular adhesions
    - Callosal dysgenesis
    - Cerebellar hypoplasia
    - Enlarged cisterna magna
    - Decreased cerebral volume

- Arthrogryposis, club foot
- Microphthalmia
- Hydrops fetalis, foetal loss

- Umbilical Artery Doppler – for intra uterine growth restriction

Pit falls in the diagnosis of microcephaly –

- Microcephaly is a progressive condition and therefore definite prenatal diagnosis is not possible in most cases.
- About 80% of infants with microcephaly have normal head circumference at birth and about 90% of those diagnosed at birth had normal cranial measurements in second trimester ultrasound. Cases diagnosed in utero represent extreme reduction in head circumference, usually with multiple anomalies.
- Pit falls in taking correct measurement – choosing incorrect section, wrong calliper placement.
- Causes of microcephaly can be different and isolated microcephaly is difficult to interpret.

Congenital Zika syndrome

Whom to suspect

- New-borns of mothers with symptoms/laboratory evidence for Zika virus infection during pregnancy.
- Prenatal USS showing evidence of foetal microcephaly, ventriculomegaly, limb defects.
- Newborn who have clinical or neuroimaging findings suggestive of Cong Zika Syndrome (CZS) and a maternal epidemiologic link suggesting possible transmission (which includes paternal exposure), regardless of maternal Zika virus test results.

How to evaluate

- Examination and follow up
- Comprehensive physical examination
- Neurological examination

- Head ultrasound within age 1 month
- Ophthalmologic exam within 1 month
- Automated ABR for Hearing by age 1 month
- Evaluate for other causes of congenital anomalies/microcephaly
- Developmental milestones monitoring
- Comprehensive physical examination at birth
- How to measure Head circumference
- Use a non-stretchable measuring tape
- Securely wrap the tape measure around the widest possible circumference of the infant's head
- Typically, 1–2 finger-widths above the eyebrow (supraorbital ridges) on the forehead, above the ears, to the most prominent part of the back of the head (occiput)
- Inaccurate measurements are often recorded on day 1 in the newborn because of several factors (e.g., scalp oedema, cephalohematoma, moulding), and repeat measurement may be indicated.
- Microcephaly (defined as Head circumference less than 2 SD or 3rd centile on standard growth charts) (e.g., WHO growth reference charts if GA >=37 weeks and Intergrowth-21st/ Fenton reference charts for GA 24– 36 weeks)
- Severe microcephaly is defined as head circumference less than 3 Std deviations.

Others

- Growth retardation (weight below 10th centile for gestation)
- Congenital limb contractures
- Dysphagia
- Sensorineural hearing loss
- Epilepsy

- Abnormalities of tone or movement

Ophthalmologic exam (Before 1 Month of Age)

Ophthalmological features

- Microphthalmia
- Coloboma
- Macular scarring with focal pigmentary retinal mottling
- Intraocular calcifications
- Optic nerve hypoplasia and atrophy
- Cortical visual impairment

Others

- Growth retardation
- Congenital limb contractures
- Dysphagia
- Sensorineural hearing loss
- Epilepsy
- Abnormalities of tone or movement
- Postnatal hydrocephalus

Head ultrasound

Radiological signs

- Intracranial calcifications (most commonly at the junction between the cortical and subcortical white matter)
- Ventriculomegaly
- Cortical atrophy
- Reduced brain volume
- Simplified gyral patterns (e.g., polymicrogyria, pachygyria, lissencephaly)

- Thinning of hypoplasia of the corpus callosum
- Hypoplasia of the brainstem and cerebellum
- Increased extra-axial fluid spaces

Neurological examination

- Posture and tone
- Reflexes
- Movements
- Abnormal signs or patterns
- Orientation/behaviour
- IF abnormal neurological examination, then refer to a paediatric neurologist.

Hearing evaluation (to complete by 1 month of age)

- OAE at birth followed by automated auditory brain stem response (ABR) by 1 month of birth to detect sensorineural hearing loss.

Developmental Follow Up

- In suspect or probable cases, Follow up for developmental milestones at 3 monthly intervals till one year, then 6 monthly till 3 years of age.
- Use Development Observation card.
- If there is a delay, refer to a Developmental specialist for a detailed development assessment.

Laboratory tests

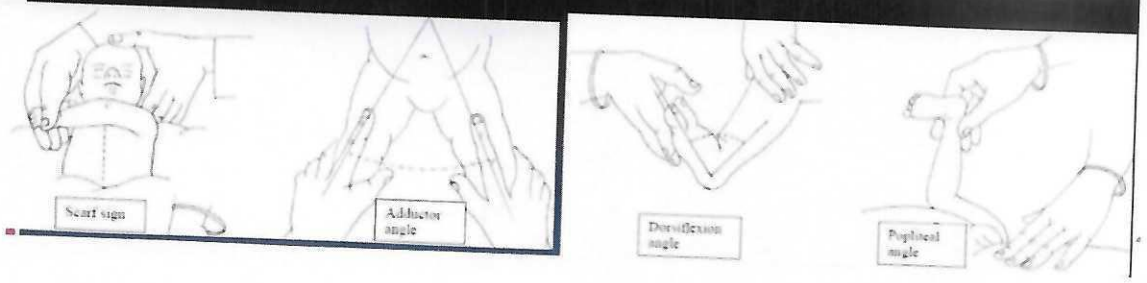
- Evaluation for Zika virus RNA in infant serum and urine, preferably within 1 week of life. (Virus persists on average 2 weeks longer in urine)
- Zika virus IgM antibodies in serum.
- If cerebrospinal fluid (CSF) is obtained for other purposes, NAT and IgM antibody testing should be performed on CSF
- Evaluate for other causes of congenital anomalies/microcephaly, Including TORCH screen

Interpretation

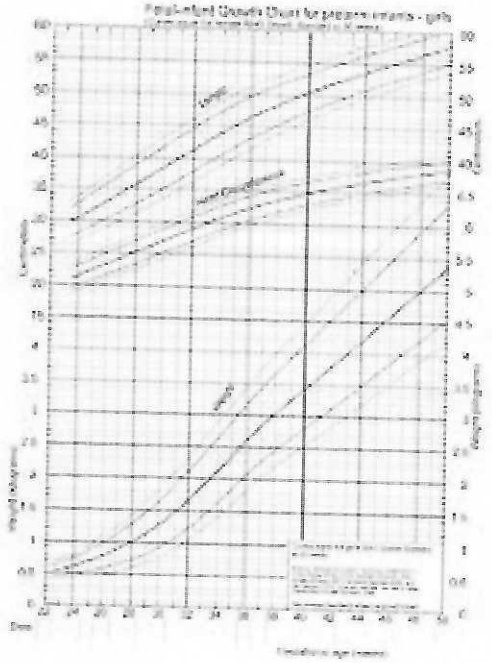
- Zika virus NAAT positive result in an infant sample confirms the diagnosis of congenital Zika virus infection.
- Zika virus IgM detected in an infant with a negative NAAT result should be interpreted as a probable congenital Zika virus infection.
- If neither Zika virus RNA nor Zika IgM antibodies are detected on the appropriate specimens (e.g., serum or urine) obtained within the first few days after birth, congenital Zika virus infection is unlikely.

Muscle tone norms (Ameil Tison)

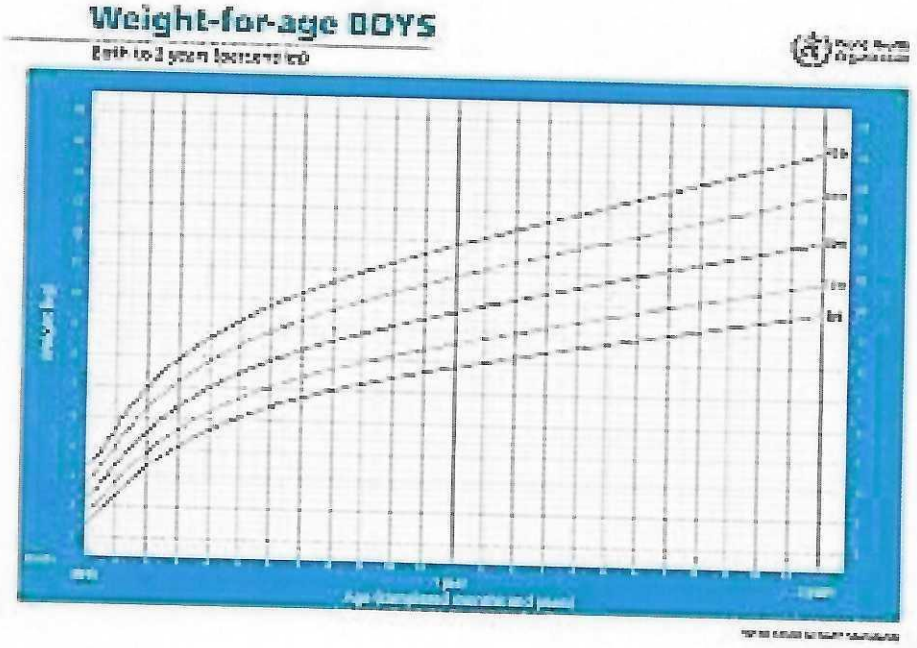
Age (months)	Adductor angle	Popliteal angle	Dorsiflexion angle	Scarf sign
0-3	40° -80°	80° -100°	60° -70°	Elbow does not cross midline
4-6	70° -110°	90° -120°	60° -70°	Elbow crosses midline
7-9	110° -140°	110° -160°	60° -70°	Elbow goes beyond axillary line
10-12	140° -160°	150° -170°	60° -70°	



Fenton's Growth Chart for Preterm

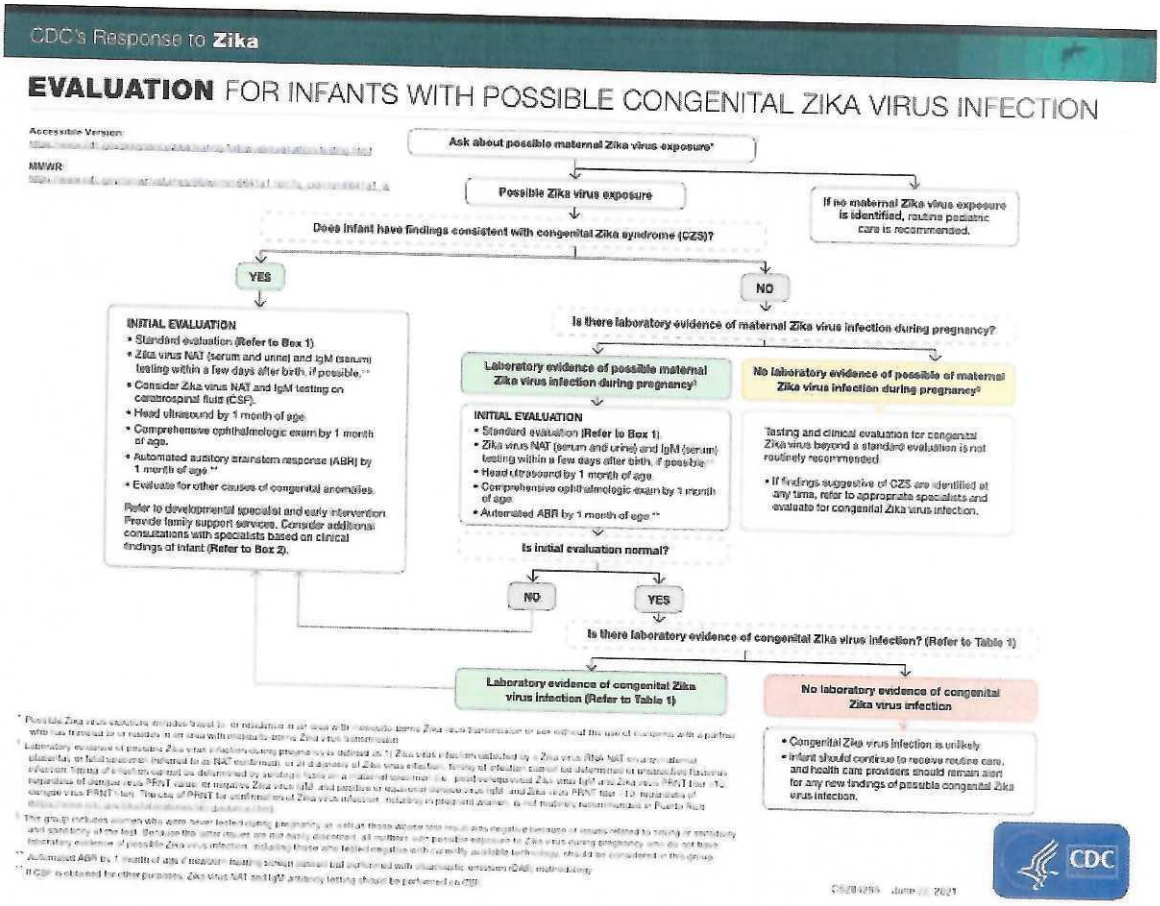


WHO growth charts for term babies



Development Observation Card

Developmental milestones	Attained age
Social smile	2 months
Holds head steady	4 months
Sits alone	8 months
Stands alone	12 months
Make sure that baby does **see, hear and listen**	



Antenatal ultrasound guidelines for Zika viral disease

- Algorithm for follow up of suspected/proven antenatal neonates: Timing: First day of life – Neurosonogram
- If not resolved by Neurosonogram – MRI Brain CT Brain for confirmation of calcification.

Protocol for Zika diagnosis

Samples to Be Collected for Zika PCR

- Blood (within seven days of onset of symptoms)
- Urine (7-20 days of onset of symptoms)
- CSF
- Amniotic fluid Depending on the clinical condition
- Serum –IgM Zika and PRNT- sample will be sent to NIV Pune
- 5ml of blood sample is to be collected from the patient within seven days of

symptom onset and transported to the lab in a triple packaging system maintaining the cold chain as soon as possible. All samples should be accompanied by the filled Sample Referral Form for Zika virus available in the Department of Microbiology, Govt. Medical College and DMO office, Trivandrum.

- Urine sample is to be collected from patients within 7-20 days of onset of symptoms. 5ml urine must be collected in a sterile container and transported considering all the precautions for the blood sample.

Storage

- Keep the sample refrigerated (2-8oC) if it is to be processed (sent to reference lab) within 48 hours.
- Keep frozen (-10 to -20oC) if it is to be processed after the first 48 hours or within seven days.
- Keep frozen (-20oC) if it is processed after a week. The sample can be preserved for an extended period.
- In the laboratory, serum separation is done, and the sample is aliquoted in three cryovials — one for testing, one for back up and one to send to NIV, Pune. The sample tested positive for ZIKA virus PCR are send to NIV, Pune and 50 samples tested negative for ZIKA virus PCR per month; samples from symptomatic pregnant women, samples from neonates with microcephaly and their mothers are also sent to NIV, Pune. Samples from children less than five years who are tested negative for ZIKA virus, Dengue Virus and Chikungunya Virus PCR are tested for IgM measles and Rubella in our laboratory itself
- ZIKA PCR tests available in GMCT, GMCK, GMC Thrissur & NIV unit Alappuzha
- Trioplex PCR -DEN, CHIK, ZIKA
- Single plex PCR- ZIKA only

Guidelines for Blood transfusion

- Blood donors with a history of fever with or without rashes are deferred for four weeks from blood donations

- Donors coming from or having a travel history to endemic areas for Zika virus infection should be deferred from blood donation for 120 days as per NBTC (National Blood Transfusion Council) guidelines.
- For transfusion of blood components to antenatal mothers in early pregnancy up to 20 weeks where pregnancy is bound to continue and for cases of organ transplantations, blood units (in areas with local transmission) should be screened for Zika virus infection by RT-PCR testing.
- Consent from the patient side should be collected before the transfusion of blood components unscreened for Zika virus infection for patients of the category as mentioned above in emergencies
- Zika virus screening for all blood units is not indicated in the current situation.

Guidelines for transplantation

- The full scope of implications of the Zika epidemic to organ transplant recipients and candidates is not yet known; however, it is expected that these patients will be affected. The impact of Zika infection in solid organ recipients are not explained. There is a possibility that clinical manifestations in these patients may be different due to immunosuppression and end-organ dysfunction. Another area of concern is transmission through organ donation. Therefore, the transplant community must be prepared to deal with this threat. The following recommendations are suggested.

Variable	Recommendations
Transplant recipients and candidates	
Living in an area of Zika transmission	Use protective measures to avoid mosquito bites, such as the use of insect repellents, long-sleeved shirts and pants, and mosquito nets
Not living in an area of Zika transmission	Avoid unnecessary travel to areas with Zika transmission If travel cannot be avoided, use protective measures to avoid mosquito bites, such as the use of insect repellents, long-sleeved shirts and pants, and mosquito nets
Living donor in areas without Zika transmission	

Variable	Recommendations
Asymptomatic living donors with a history of travel to an area of Zika transmission	Defer donation for four weeks after return. If no symptoms develop in 4 weeks, may donate after a discussion about the risk and benefits of potential donor-derived infection and informed consent
Living donors with Zika virus infection	Defer donation for six months after the onset of symptoms. If the recipient's clinical condition does not allow the delay in transplantation, obtain Zika virus PCR 4 weeks after resolution of symptoms, and consider donation only if PCR is negative and after discussion of risk and benefits of potential donor-derived infection and informed consent
Living donor in areas with Zika transmission	
Living donors with Zika virus infection	Defer donation for six months after the onset of symptoms. If the recipient's clinical condition does not allow the delay in transplantation, obtain Zika virus PCR 4 weeks after resolution of symptoms, and consider donation only if PCR is negative and after discussion of risk and benefits of potential donor-derived infection and informed consent
Asymptomatic living donors	Discussion about potential risk with recipients. Donors should counsel on measures to avoid infection, such as measures to avoid mosquito bites and consistent and correct use of condoms during sex, until the donation
Deceased donor in areas without Zika transmission	
Asymptomatic donor with travel to an area of Zika transmission in the preceding four weeks	May be considered for organ donation after the discussion about the risk and benefits of potential donor-derived infection and informed consent
Donor with symptoms suggestive of Zika virus infection and with travel to an area of Zika transmission in the preceding six months	Do not use donor organs unless symptoms can be attributed to a condition other than the Zika virus, and this other condition does not preclude donation
Deceased donor in areas with Zika transmission	

Variable	Recommendations
Asymptomatic donor	May be considered for organ donation after a discussion about the risk and benefits of potential donor-derived infection and informed consent
Donor with symptoms suggestive of Zika virus infection in the preceding six months	Do not use donor organs unless symptoms can be attributed to a condition other than the Zika virus, and this other condition does not preclude donation

NB -There is limited data on the length of time the virus persists in tissues. Because up to 80% of infections can be asymptomatic, living donors residing in ZIKV-affected areas may be screened for Zika virus infection using PCR (For kidney donors, it is better to screen for virus in urine sample also.) Recipients of such donors should be monitored carefully in the first months after transplant. The potential impact of the Zika virus in the immunosuppressed solid organ transplant recipient on graft rejection and infectious complications are not known. Blood transfusions may be limited to compelling indications and may be screened for ZIKA virus before transfusion to the transplant recipients.

Annexure: Centralized training plan to the public health workers

- In the scenario of reporting of Zika cases in Kerala, the situation needs intensified preparation in the containment and management of Zika virus spread, as the Zika virus transmits through the Vector transmission mode; the effective public health strategies enforced on the perfect vector control and management will lead the better containment of the disease. To prepare the workforce (Field health workers) to combat the situation, KHISFW is instructed to take the following steps for the training and capacity building of field health staff. The training was designed in a manner of centralized dissemination to enforce the creation of strengthened TOT's around the state. State training division NHM may conduct the TOT session before 15/7/21, and the dissemination activity by SIHFW should start from 17/7/21. The entire activity should be monitored by Additional Director Administration and training

General Instructions for Training Conduction

- The training sessions should be conducted in an online live interactive manner. All batches should land on the question & answer session.
- As the institute was instructed to start in online mode, start the sessions and batches in an emergency manner/Urgent basis.
- The proposed schedule and terms of faculty selection are attached to this document.
- Conduct at least two sessions per day (2 batches)
- The districts, Institutions should be informed through a prior communication and ensure the adherence of participants.
- The program's attendance should be collected through online modalities such as Google form – The same should be cross-checked by Online in time camera surveillance and cross-checking with concerned charge officers of peripheral institutions. The summary with enclosed details of attendance should be communicated to this office in due time.
- State Training Division, NHM, may provide the team with the available AV Aids and PPTs after TOT
- All sessions should be ended in a post-training test with minimal questions (Not less than 15) through an online modality. The attendance of the posttest should be

correlated with the session attendance.

- The materials should be communicated to the institutions/Participants in mail ID's
- An adequate number of batches should be conducted to cover the entire state workforce (Field health workers).
- Create many faculty pools with the following specifications as per schedule. The number of faculty pools should be sufficient to run the training process uninterruptedly.
- A sample schedule for the training conduction is attached with this document

Proposed Curriculum for the Training

Sl no	Session	Content of the topic	Duration	Faculty
1	Session I	Introduction to Zika Virus infection, Epidemiology, Burden of the disease, Effect on community, Need for containment	20 Minutes	Faculty from the medical fraternity
2	Session II	Disease aspect – Definition, Causative organism, Risk groups, Signs and symptoms, diagnosis, symptomatic management	30 Minutes	Faculty from the medical fraternity
3	Session III	Disease aspect – Complications, Community surveillance strategies, screening, testing strategy, control, and prevention measures	30 Minutes	Faculty from the medical fraternity
4	Session IV	Integrated vector control and management	45 Minutes	Specialist – Entomology
5	Question and answer session		10 Minutes	Combined faculty panel
6	POST-TEST		10 Minutes	Online modality

Objectives of the training

- After the training program, the participants will be able to acquire knowledge/refresh the knowledge regarding Zika virus disease and control measures with a positive attitude in practising that knowledge in various practice settings (Community, Field settings, Institutions, Clinical areas etc.)

Specific objectives

- **Session I** – The group will get introduced to the topic – Zika virus infection, Epidemiology, and burden of the disease
- **Session II** – The group will be able to explain the disease aspects of the Zika virus infection - Definition, Causative organism, Risk groups, Signs and symptoms, diagnosis, symptomatic management
- **Session III** – The group will be able to describe the disease aspect of Zika virus – Reducing community impact - Complications, Community surveillance strategies, screening, testing strategy, control, and prevention measures
- **Session IV** - The participants will be able to demonstrate skills in integrated vector control and management
- **Method of training** - Online interactive live sessions in successive batches
- **Duration of the training** – 2 Hr 30 Minutes
- **Target group** – HS, HI, JHI, PHN, LHI, JPHN, ASHA etc

Model Schedule for Training

Sl no	Day	District/batch	
1	Day I	Morning	Trivandrum 1st batch
		Afternoon	Trivandrum 2nd batch
2	Day II	Morning	Kollam 1st batch
		Afternoon	Alappuzha 1st batch
3	Day III	Morning	Pathanamthitta 1st batch
		Afternoon	Idukki 1st batch
4	Day IV	Morning	Kottayam 1st batch
		Afternoon	Ernakulam 1st batch
5	Day V	Morning	Thrissur 1st batch
		Afternoon	Palakkad 1st batch
6	Day VI	Morning	Malappuram 1st batch
		Afternoon	Kannur 1st batch
7	Day VII	Morning	Kozhikkode 1st batch
		Afternoon	Wayanad 1st batch
8	Day VIII	Morning	Kasargod 1st batch
		Afternoon	Kollam 2nd batch
9	Day IX	Morning	Alappuzha 2nd batch
		Afternoon	Pathanamthitta 2nd batch
10	Day X	Morning	Idukki 2nd batch
		Afternoon	Kottayam 2nd batch
11	Day XI	Morning	Ernakulam 2nd batch
		Afternoon	Thrissur 2nd batch
12	Day XII	Morning	Palakkad 2nd batch
		Afternoon	Malappuram 2nd batch
13	Day XIII	Morning	Kannur 2nd batch
		Afternoon	Kozhikkode 2nd batch
14	Day XIV	Morning	Wayanad 2nd batch
		Afternoon	Kasargod 2nd batch