SENARAI EDARAN

YBhg. Datuk/ Dato' / Tuan / Puan,

GARISPANDUAN “THE MINISTRY OF HEALTH GUIDELINES ON ZIKA VIRUS IN PREGNANCY” DAN “GUIDELINE ON THE MANAGEMENT ZIKA VIRUS-RELATED GUILLAIN-BARRÉ SYNDROME (GBS)”


Sekian.

"BERKHIDMAT UNTUK NEGARA"
Saya yang menurut perintah,

(DATUK DR NOOR HISHAM BIN ABDULLAH)
Ketua Pengarah Kesihatan
Kementerian Kesihatan Malaysia

s.k.

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The Ministry Of Health Guidelines on Zika Virus in Pregnancy

Introduction

Zika infection was declared by World Health Organization (WHO) as a health emergency of international concern in February 2016. This was following the outbreak in Brazil in May 2015 following which there was a sudden increase in the incidence of microcephaly.

As of August 2016, 70 countries have reported evidence of vector borne Zika infection; including Singapore in recent weeks, with endemic transmission in four countries. These numbers are expected to increase with time; especially in countries where Aedes mosquitoes are highly prevalent.

Malaysia reported its first Zika infection in pregnancy on 7th September 2016.

This guideline is based on the current evidence; changes will be made as when new data and evidence emerges.

Zika Virus

Although it was accidentally discovered in 1947 in Uganda, the first human transmission was documented in 1953 and Zika virus was isolated in Borneo in 1963. In September 2014 a tourist was found to be infected with Zika after travelling in Sabah. Despite multiple sporadic infections which were usually mild and self-limiting within Asia and Africa, and two major endemics in 2007 & 2013, it remained a relatively unknown infection till May 2015.

It is a mosquito borne flavivirus, a single stranded RNA virus. Aedes Aegypti, a mosquito which is a household name in Malaysia, is the main vector. This mosquito also spreads Dengue and Chikungunya. A. Albopictus on the other hand is a more common vector in the western world. The mosquito is active during the day and breeds indoors.

There is molecular evidence based on genotyping that the current endemic throughout South and Central America originated from Asia. The impact of globalization, rapid urbanization and the contributions of the tyre industry in harbouring and transmitting these mosquitoes across the globe is an interesting fact and it has been postulated that the sudden endemic could be possibly due to a new genetically adapt and virulent strain or a population which has previously been naïve to this virus.

Transmission

Four possible mechanisms of transmission has been proposed. Mosquito bites from infected persons are the most common mechanism of transmission. A. Aegypti is a mosquito with high vectorial capacity. It feeds primarily on humans and often bites
multiple times in a single blood meal. It breeds indoors, lives with close association with human habitation and has an imperceptible bite.

A sylvatic transmission cycle between non human primates via forest dwelling species of *Aedes* are postulated as a mechanism which is unique to Africa. In most other countries, especially in urban and suburban environments, a human-mosquito-human transmission cycle is the common mode of transmission.

Transmission from mother to child has also been reported as Zika virus has been cultured in amniotic fluid based on numerous case reports. Zika virus has also been isolated in brain tissues and placentas of pregnancies that unfortunately ended in miscarriages and stillbirths perceived to be associated with Zika infection. Recently, there have also been documented case reports of peripartum transmission of Zika virus.

There is now concrete evidence that it can be sexually transmitted, especially in men who were symptomatic as the virus can be detected in semen up till 62 days.

Despite no documented evidence of infection via blood, it remains a theoretical risk.

Although it also has been detected in urine and saliva, the risk of transmission via these bodily fluids remains unknown. There have been 4 documented cases of transmission via laboratory exposure although the exact nature of transmission remains unknown. Thus, universal measures are recommended when in contact or during handling of such samples.

As of today, there has not been any documented transmission via breast feeding and thus it is not contraindicated even among infected mothers.

**Signs and symptoms**

80% of patients are asymptomatic and the exact incubation period for Zika infection is unknown, although generally accepted to be less than a week.

**Rash, conjunctivitis and arthralgia** are the most significant symptoms although most of these symptoms are self-limiting; lasting between 2-7 days. Other common symptoms include headache, fever and itching.

**Diagnosis**

The recommended diagnostic test is Zika viral nucleic acid (NAT) test via reverse transcription polymerase chain reaction (RT-PCR).

Although Zika has been detected in blood, amniotic fluid, semen, urine and saliva, the mainstay of confirmation for Zika is limited to whole blood and urine. These tests are readily available in almost all tertiary hospitals in Malaysia and at the Institute for Medical Research (IMR). These services are also provided by a few private laboratories. The results will be available between 2-4 days.

The Zika virus is found in the plasma for a very short window of time where the levels peak at day 3 and significantly drops from day 7 onwards. Hence the test is
highly sensitive within the first 7 days from the onset of symptoms. Zika is on the other hand detected in urine for a longer period of time; which is up till 14 days. So, in patients who fulfil the case definition for Zika fever and are within the first 7 days from the onset of symptoms should have their blood and urine checked while those between day 8-14, it is recommended to check their urine alone. These tests are not sensitive if done beyond 14 days from the onset of symptoms.

Although serological testing via plaque-reduction neutralization tests (PRNT) has been advocated to have higher sensitivities as compared to other serological methodologies, serological testing is not recommended in view of cross reactivity with other similar viruses, especially dengue which is highly prevalent in Malaysia.

Testing for Zika virus in the amniotic fluid in pregnancy remains controversial as the presence of virus in the amniotic fluid does not correlate with the severity or the degree of infection. Hence amniocentesis as confirmation of perinatal infection is not recommended as routine.

The viral antigen and RNA can also be isolated from the placenta and umbilical cord and this is recommended in the event of a stillbirth or as part of post-delivery confirmation in suspected cases, although this test is yet to be available in Malaysia at this moment.

**Prevention**

i) **Prevention of mosquito bite**

Pregnant mothers should be advised against travel to Zika endemic areas. Staffs should be trained to identify Zika prone areas and these territories and countries are constantly updated in the WHO, CDC and PAHO websites on a regular basis.

The use of long and loosely fitted trousers and sleeves, apart from clothing treated with insecticides such as permethrin are recommended as an effective measure. Sleeping using nets impregnated with permethrin and using N, N-diethyl metatoluamide (DEET) based repellents are also the recommended measures of bite prevention. These insecticides and repellents are safe to be used among pregnant mothers.

ii) **Prevention of sexual transmission**

There is growing evidence that Zika can now be sexually transmitted. Women should be advised against traveling to zika endemic areas. If either the women or men have recently returned from Zika endemic areas, barrier contraception should be used for at least 28 days.

However if the men are symptomatic, the virus remains longer in sperm and barrier methods of contraception should be used for at least 6 months. The risk of transmission has been proven during vaginal, anal or oral sex without a condom.

Although there recently has been a news report about the possibility of women transmitting the infection to her partner, there is inconclusive evidence to verify this, similarly with the risk of transmission via kissing and the mouth-vaginal route.
Treatment

There is no antiviral treatment which is available at the moment. Management is purely based on symptomatic treatment and surveillance for potential complications.

Management in pregnancy

1. Pregnancy has to be planned and to avoid mosquito bites as much as possible during pregnancy.

2. Women with a history of blood/blood products transfusion is advised to avoid pregnancy for 8 weeks post transfusion.

3. The recommended method of contraception is the barrier method.

4. Women with a history of travelling to a Zika endemic area and is symptomatic must be screened for Zika virus infection.

5. Men with a history of travelling to a Zika endemic area and is symptomatic – must have protected sex for the next 6 months. If the man is travelling frequently to Zika affected areas and has a pregnant partner, he is advised to have protected sex throughout the pregnancy period.

6. Supplement information with information leaflet, posters and brochures.

7. Discuss risk of Zika infection in pregnancy.
   7.1 Maternal risk
       • The mother has a risk of developing Guillain Barre Syndrome.
   7.2 Fetus risk
       • Miscarriage
       • Stillbirth
       • Preterm delivery
       • Congenital Zika syndrome

8. Amniocentesis for detection of Zika virus in amniotic fluid is not recommended as a routine.

9. Pregnant mothers with Zika virus infection need to be given the yellow tag by Klinik Kesihatan.

10. Malaysia is currently in the containment phase of Zika virus and hence, all mothers who are symptomatic should ideally be admitted and managed as inpatient. However, if this progresses to a mitigation phase in future, admission of all symptomatic mothers may not be necessary.

11. Test for Zika virus in the 1st week of illness requires 2 specimens (blood and urine specimen). Meanwhile, test for Zika virus from day 8 until day 14 of illness
requires only urine specimen (Refer to Updated Zika Alert" dan Arahan Pentadbiran untuk Pemantauan dan Pengurusan Jangkitan Virus Zika 11 September 2016; Lampiran 2A1,2A2,2A3 dan 2B Carta Alir ujian pengesahan virus Zika)

12. Delivery of women with positive Zika virus must be done in specialist hospitals

13. Universal precaution during delivery process must be observed

Complications

i) Miscarriage & stillbirths

Although the absolute risk cannot be accurately measured, there is an association that Zika infection increases the risk of miscarriage and stillbirths. This is based on the presence of Zika RNA in products of conception following miscarriages and stillbirths.

ii) Congenital Zika Syndrome

Microcephaly is defined as head circumference which is below the 2.5th centile of the population or measurements which are 2 standard deviations below the mean for that specific gestation. Growth chart and serial measurements are usually required to confirm these diagnoses.

Correct measurement of head circumference

The correct plane for measurement of head circumference must include cavum septum pellucidum, thalamus and choroid plexus in the atrium of the lateral ventricles

There is growing evidence that Zika has significant association with microcephaly as the current trends suggest more of a causal rather than an association, although the
evidence is still evolving. It is difficult to estimate the absolute risk which may be high during outbreaks but is perceived to be lower than the risk associated with Rubella or Cytomegalovirus. The risk is highest if the infection is acquired in the first trimester, being significant even until 28 weeks of pregnancy.

It is now perceived that microcephaly is the end stage measurable manifestation of the disease while other possible ultrasonographic features of congenital Zika syndrome include:

i) Intracerebral calcifications
ii) periventricular or intraventricular echogenicity
iii) irregularly shaped lateral ventricles
iv) Callosal or vermian dysgenesis
v) Posterior fossa abnormalities

iii) GullainBarre Syndrome

A temporal and geographic relationship has been observed between Guillain–Barré syndrome and Zika virus outbreaks in the Pacific and the Americas. 93% of patients with Guillain-Barre Syndrome in these populations had serological confirmation of Zika Virus. Other neurological manifestations include an increased risk of meningoencephalitis and acute myelitis.

Resources

I. WHO www.who.int
II. PAHO www.paho.org
III. CDC www.cdc.gov
IV. ECDC www.ecdc.europa.eu
V. UK GOV www.gov.uk
VII. RANZCOG www.ranzcog.edu.au
VIII. RCOG www.rcog.org.uk
IX. SOGC www.sogc.org
X. ACOG www.acog.org
XI. SMFM www.smfm.org
XII. ISUOG www.isuorg.org
Flowchart for Management of Zika Virus in Pregnancy

Pregnant woman fulfilling clinical case definition of suspected case of Zika virus infection (refer to “Updated Zika Alert” dan Arahan Pentadbiran untuk Pemantauan dan Pengurusan Jangkitan Virus Zika 11 September 2016)

Presented within 7 days from onset of symptoms

Pre-test counseling

Test for Zika virus infection (RT-PCR)

Positive Zika virus infection

Notify nearest Pejabat Kesihatan

Post-test Counselling

Refer Klinik Pakar O&G

- Fetal ultrasound to detect features of congenital Zika syndrome
- 4 weekly growth scans at 28, 32 and 36 weeks. Minimum 2 scans
- Monitor pregnancy (until delivery)
- Placental & Umbilical cord HPE (post-delivery) whenever feasible and available

Negative Zika virus infection

- Continue ANC follow up at klinik kesihatan

Post-test Counselling

Patient information leaflet to Pregnant women

Baseline ultrasound *(Include BPD, HC, AC, FL)

- 4 weekly growth scans at 28, 32 and 36 weeks.
- Minimum 2 scans

Presence of microcephaly (HC < 2.5th of population)
Or
Intracranial/placental calcifications

Absence of microcephaly

Refer newborn to Pediatrician post-delivery for further management

i) Presented beyond 7 days and is no longer symptomatic
ii) Asymptomatic pregnant women with exposure

*BPD : Biparietal diameter
HC : Head circumference
AC : Abdominal circumference
FL : Femur length
HPE : Histo pathology examination

*This flowchart will be reviewed during the mitigation phase

7
Pre & Post test counselling

1) The general principles of counselling, which includes a verbal consent and maintaining confidentiality should be adhered too.

2) The benefits and limitations of the test which is ideally done within the window period should be discussed with the patient and it is essential to ensure the correct results are given to the correct patient. The implications of a positive or a negative test should also be discussed.

3) If the test is negative, the risk of contracting Zika in future and the importance of prevention should be highlighted.

4) The patient or her partner has the right to refuse the test or the right not to know the results and this should be documented in the notes.

5) Mandatory testing is not warranted.

6) Re-testing may be necessary if the patient reports symptoms with a substantial exposure to Aedes mosquito.

Termination of pregnancy

Congenital Zika syndrome per se is not an indication for termination of pregnancy. This is also in accordance to the current and available law and regulations with regards to termination of pregnancy in Malaysia. (http://www.moh.gov.my/images/gallery/Garispanduan/Guideline%20On%20TOP%20for%20Hospitals%20in%20MOH.pdf)

Each and every case where TOP is considered has to be dealt in accordance with the existing Ministry of Health TOP guidelines.
Protocol for Blood Transfusion in Pregnant Women and Other ‘At-Risk Transfusion Recipients’ In Relation To Zika Virus Infection

The Zika virus (ZIKV) has been linked to microcephaly in children born to infected mothers, as well as blindness, deafness, seizures and other congenital defects. Although ZIKV is mainly transmitted through mosquito bite, the virus may also present a risk to blood safety as non-vector transmission is possible.

It has been reported that during the ZIKV outbreak in French Polynesia between November 2013 and February 2014, 2.8% of the asymptomatic blood donors were confirmed positive for Zika virus RNA. Since then, there has been at least one report of ZIKV infection acquired through blood transfusion in Brazil\(^1\). This report also is supported by evidence for transmission of ZIKV by platelet transfusion in 17 August 2016\(^2\).

Ideally the blood supply during active transmission of Zika should be maintained by increasing blood collections in non-affected areas. Potential donors should be counselled and temporarily deferred, if required, based on the risk of ZIKV exposure.

**Priority for the use of ZIKV screened blood during active transmission of ZIKV should be given to pregnant women who required blood transfusion during antenatal period. If possible this ZIKV screened blood also be given to other ‘at-risk transfusion recipients’**

1. The following are the categories of at-risk transfusion recipients:
   i. Ideally ALL pregnant women in the antenatal period who require blood transfusion.
   ii. Women in the reproductive age group who are transfusion dependent (eg Thalassaemia) and are planning to start for their family.
   iii. All intrauterine transfusion

2. Common conditions of patients who may require Zika screened negative blood and blood products in the antenatal period.
   i. Severe anaemia including women with thalassaemia
   ii. Severe antepartum hemorrhage
   iii. Placenta praevia

3. Effort should be made in the pre-conception period and antenatal management/care for the prevention, early diagnosis and effective treatment of anaemia that could result in the need for transfusion in all women in the childbearing age.

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\(^1\)Zika virus: a new challenge for blood transfusion, published online May 3, 2016, [http://dx.doi.org/10.1016/s0140-6736 (16)30428-7](http://dx.doi.org/10.1016/s0140-6736 (16)30428-7)

4. There should be strict adherence to available guidelines and blood should be used judiciously on a need for basis especially in the antenatal period to avoid unnecessary transfusion. As part of optimal patient blood management, alternatives to blood transfusion should be made available including
   i. Pharmaceuticals such as oral and parenteral iron
   ii. Medical devices
   iii. Good surgical and anaesthetic techniques.

Availability and Management of ZIKV Screened Negative Blood

1. It is estimated that around 5 – 10 % of all pregnancy in a year may require red cell transfusion in the antenatal period, i.e. around 25,000 – 50,000 women. And each patient on average may need 2 units of red cell thus a total of 50,000 – 100,000 units of ZIKV screened blood for transfusion may be required each year (around 130-200 units every day).

2. Considering the available expertise, infrastructure and turnaround time required for the adequate and timely supply of Zika screened blood; it is proposed that the screening of donated blood for ZIKV is to be conducted in Pusat Darah Negara (PDN). The screened blood will be labelled as 'ZIKA SCREENED NEGATIVE BLOOD' and will be distributed by PDN to all the State Hospitals on a regular basis.

3. There will be scheduled distribution to selected hospitals based on the workload and historical transfusion data in antenatal patients if available. The allocation of blood is estimated to cover roughly 5% of the total annual deliveries.

4. Each of the State Hospital will then distribute the blood to the other hospitals in the state and monitor the availability of the stock through the 'Malaysian Blood Stock System' at http://pdn.gov.my/mybss/ on a regular basis. The following are the list of hospitals that will be keeping a stock of ZIKV screened blood on regular basis.

   i. Hospital Tuanku Fauziah, Kangar, Perlis
   ii. Hospital Sultanah Bahiyah, Alor Setar, Kedah
   iii. Hospital Pulau Pinang, Pulau Pinang
   iv. Hospital Raja Permaisuri Bainun, Ipoh, Perak
   v. Hospital Tengku Ampuan Rahimah, Klang, Selangor*
   vi. Hospital Tuanku Jaafar, Seremban, Negeri Sembilan.
   vii. Hospital Melaka, Melaka.
   viii. Hospital Sultanah Aminah, Johor Baru, Johor
   ix. Hospital Tuanku Ampuan Afzan, Kuantan, Pahang
x. Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu

xi. Hospital Raja Perempuan Zainab, Kota Bharu, Kelantan

xii. Hospital Queen Elizabeth, Kota Kinabalu, Sabah

xiii. Hospital Umum, Kuching, Sarawak

xiv. Hospital Kuala Lumpur.

_PDN will also be providing the blood to KKM hospitals in the Klang Valley that take their blood stock directly from its premise for logistics coordination._

5. The decision for transfusion should be made on a need for basis, based on the clinical circumstances and the advice from the transfusion specialist or haematopathologist in charge of blood bank may be sought if there are further concerns.

6. The request form will be label as **REQUEST FOR ZIKA SCREENED NEGATIVE BLOOD.**
Flowchart for 'Zika Screened Negative Blood' Requests For Pregnant Mothers

Identify pregnant woman at risk of requiring transfusion in the antenatal period

1) Workup for anaemia
2) Optimize haemoglobin by giving oral or IV iron

Decision to transfuse must be made by O&G specialist with strict criteria:

a) Severe antepartum haemorrhage
b) Severe anaemia including thalassaemia
c) Placenta Previa

O&G specialist must counsel and get consent for transfusion

O&G specialists must inform and discuss with Transfusion Specialist/Head of State Transfusion Service/PDN to request for ZIKA SCREENED NEGATIVE BLOOD

Requests form shall be completely filled with the indication and labelled with (REQUEST FOR ZIKA SCREENED NEGATIVE BLOOD)

Transfusion Specialist to monitor stock for ZIKA SCREENED NEGATIVE BLOOD

TRANSFUSION

RECORD AND DOCUMENTATION
Initial Evaluation and Management of Newborn with Possible Congenital Zika Virus Infection

Mothers fulfilling clinical case definition of Zika Virus infection

Does mother have lab evidence of Zika virus infection

MOTHER NOT TESTED OR TESTED OUTSIDE OF APPROPRIATE WINDOW

Does infant have abnormalities consistent with congenital Zika syndrome?

YES

Outpatient Management:
- Admit paediatric ward
- Routine newborn care: physical exam, including head circumference, weight, length, and neuro exam
- Head ultrasound appointment
- Infant testing for congenital Zika virus infection (blood and urine)
- Investigation for causes of microcephaly/abnormal CNS findings
- Ophthalmology exam at birth and 3 months of age
- ABR – follow audiology guidelines for high risk neonatal hearing screening
- For further neuroimaging studies appointment
- Thyroid screen (TSH & T4) at day 5-7 of life

Outpatient Management:
- Admit paediatric ward
- Routine newborn care: physical exam, including head circumference, weight, length, and neuro exam
- Head ultrasound appointment
- Infant testing for congenital Zika virus infection (blood and urine) at < 2 days of life

NO

Outpatient Management:
- Admit paediatric ward
- Routine newborn care: physical exam, including head circumference, weight, length, and neuro exam
- Head ultrasound appointment
- Infant testing for congenital Zika virus infection (blood and urine)
- Investigation for causes of microcephaly/abnormal CNS findings
- Ophthalmology exam at birth and 3 months of age
- ABR – follow audiology guidelines for high risk neonatal hearing screening
- For further neuroimaging studies appointment
- Thyroid screen (TSH & T4) at day 5-7 of life

Outpatient Management:
- 6 weeks: Follow up paediatric clinic at 6 weeks
- 3 months: Thyroid screen (TSH & T4)
- Ophthalmology exam
- ABR exam
- Routine preventive health care including monitoring of feeding and growth and immunization (continue follow up at Klinik Kesihatan)
- Routine and congenital infection-specific anticipatory guidance
- Referral to specialists, including evaluation of other causes of congenital anomalies as needed
- Referral to early intervention services

Abbreviations: ABR: auditory brainstem response
Definition

Microcephaly in newborns is defined as:

1. Occipitofrontal circumference (OFC) below or at -3SD according to WHO/CDC Growth Chart for term infants (Appendix 1)

   1.1 For term infants (POG 37-42 weeks):
      a) Full term females : OFC 30.3 cm
      b) Full term males   : OFC 30.7 cm

   1.2 For pre-term neonates (POG <37 weeks), INTERGROWTH-21 Size at Birth Reference Charts should be used (http://intergrowth21.tghn.org/articles/intergrowth-21st-very-preterm-size-birth-reference-and-z-scores-standard-deviations/)

2. Where the OFC is disproportionately smaller than the length and weight or the head is disproportionately small compared to face.

There is no uniform definition for microcephaly in newborns. Some define it as an OFC below 2 SD of the mean for age and gender, others as an OFC below 3 SD of the mean (AAN 2009, Woods 2013). In the Zika outbreak microcephaly is defined as an OFC ≥ 3 SDs below mean for age and sex. However accurate measurements need to be taken and babies with OFC below the 2 SD should be reviewed by a paediatric team. For purposes of uniformity a full term infant with an OFC ≤ 32 cm should be referred to the Paediatric Department for confirmation and assessment.

Accurate Head Circumference (OFC) Measurement Method

1. Neonates should have their head circumference measured in the first 24 hours of life.
2. A flexible non-stretchable measuring tape is to be used with 1 cm increment (A "lasso-o" tape is ideal).
3. Head circumference (OFC) is the measurement of the neonate's head which has the largest diameter.
4. Place the head circumference tape around the neonate’s head so that the tape lies across the frontal bones of the skull, slightly above the eyebrows (at the supraorbital ridges), perpendicular to the long axis of the of face, above the ears, and over the occipital prominence at the back of the head so that the maximum circumference is measured.
5. Move the tape up and down over the back of the head to locate the maximum circumference.
6. Tighten the insertion tape so that it fits snugly around the head circumference and compresses the hair and underlying soft tissues. The tape should be on the same plane on both sides of the head and tight enough to compress the hair and overlying soft tissues.
7. Repeat the OFC measurement three times and take the largest measurement.
8. Record the measurement on the data collection sheet to the nearest 0.1cm. Ensure that the recording is accurate and legible.

**Congenital Zika Syndrome is defined as:**

In addition to congenital microcephaly, a range of manifestations including craniofacial disproportion, spasticity, seizures, irritability, brainstem dysfunction such as swallowing problems, limb contractures, hearing and ocular abnormalities, and brain anomalies detected by neuroimaging have been reported among neonates where there has been in utero exposure to Zika virus.

Reported neuroimaging findings include cortical/subcortical calcifications, cortical malformations, simplified gyral pattern/migrational abnormalities, brainstem/cerebellar hypoplasia, and ventriculomegaly. While congenital microcephaly was the sign that first raised attention to the effect of Zika virus on the developing fetus, in up to one in 5 cases, some of these neurological abnormalities have occurred without associated microcephaly and have become evident only following birth. The abnormalities consistently reported in these infants, including abnormal neuroimaging findings, suggest that a congenital syndrome, akin to congenital rubella or cytomegalovirus (CMV) infection, is attributable to in utero Zika virus infection.

Based on a review of observational, cohort and case control studies, there is no strong scientific consensus that Zika virus is a cause of microcephaly and other neurological complications that together constitute a congenital Zika virus syndrome.

Longer term clinical follow-up of infants born to women with a history of confirmed Zika virus infection at different times during pregnancy is needed. Until further data becomes available, it would also be prudent to treat the affected neonate's urine and saliva as potentially infectious for at least 2 months after birth.
**Clinical Evaluation & Management of Infants with Laboratory Evidence of Zika Virus Infection**

<table>
<thead>
<tr>
<th>Multi-specialty consultation that may be required</th>
<th>Evaluations that may be required</th>
</tr>
</thead>
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<tr>
<td>1 Neurology</td>
<td>• Determination of appropriate neuroimaging and additional evaluation including audiology assessment</td>
</tr>
<tr>
<td>2 Infectious disease</td>
<td>• Diagnostic evaluation of other congenital infections (e.g. syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infection).</td>
</tr>
</tbody>
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| 3 Ophthalmology                                  | • Comprehensive eye examination and evaluation prior to discharge from hospital or within 1 month of birth.  
  • Retina evaluation for macular pigment mottling, macular chorioretinal atrophy, optic nerve hypoplasia, increased cup-to-disc ratio, iris coloboma, and lens subluxation. |
| 4 Audiology                                      | • Audiology assessment as per high risk newborn. To check for hearing loss before discharge and for evaluation at 3 months and subsequently 3-6 monthly |
| 5 Endocrinology                                  | • Evaluation for hypothalamic or pituitary dysfunction. |
| 6 Clinical geneticist                            | • Evaluation of other causes of microcephaly or other anomalies if present |
| 7 Orthopaedics                                   | • Management of hypertonia, club foot or arthrogrypotic-like conditions. |
| 8 Pulmonologist / otolaryngologist               | • Concerns about aspiration |
| 9 Lactation specialist                           | • Management of feeding issues |
| 10 Nutritionian                                  | • Early intervention services for developmental issues |
| 11 Gastroenterologist                            | • Psychosocial support |
| 12 Speech / Occupational therapist               |                                  |
| 13 Developmental specialist                      |                                  |
| 14 Medical social support service                |                                  |
Head circumference-for-age GIRLS
Birth to 13 weeks (z-scores)

WHO Child Growth Standards
**Recommendations for screening, assessing, and managing neonates and infants in areas of Zika virus transmissions**

<table>
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<tr>
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<th>Recommendation</th>
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| 1 | Neonates should have their head circumference measured in the first 24 hours of life:  
  a. For term neonates (37-42 weeks), WHO Child Growth Standards for size at birth should be used to interpret measurements. If an accurate gestational age is known, INTERGROWTH-21 Size at Birth Standards are preferred.  
  b. For preterm neonates, INTERGROWTH-21 Size at Birth Standards for gestational age and sex should be used to interpret measurements. |
| 2 | All mothers should be asked about clinical signs and symptoms suggestive of Zika virus infection and/or laboratory confirmation of Zika virus infection during pregnancy, including when the possible infection occurred (first, mid or final trimester). |
| 3 | Neonates should be examined to assess whether the head appears disproportionately small relative to the face (craniofacial disproportion). |
| 4 | In neonates with congenital microcephaly or in whom the head appears disproportionately small relative to the face, a full history and physical and neurological examination, including assessment of hearing and vision, should be performed in order to detect additional abnormalities potentially associated with Zika virus infection. |
| 5 | In neonates with head circumference < -2 SD and ≥ -3 SD, or where the head is disproportionately small relative to the face, (and there is no strong indication from clinical examination of a genetic or environmental cause of microcephaly) neuroimaging should be performed if:  
  a. Zika virus infection is suspected in the mother during pregnancy; or  
  b. Any neurological signs or symptoms are present. |
| 6 | In neonates with head circumference < -3 SD neuroimaging should be performed if there is no strong indication from clinical examination of a genetic or environmental cause of microcephaly. |
| 7 | When neuroimaging is indicated:  
  a. Either CT or MRI can be used.  
    - CT is satisfactory to identify neuroimaging findings suggestive of congenital Zika virus syndrome.  
    - MRI is satisfactory to identify neuroimaging findings suggestive of congenital Zika virus syndrome, and may also provide further detail and diagnose other conditions.  
  b. If CT or MRI are not available, cranial ultrasound can be performed if the anterior fontanelle is of adequate size. |
| 8 | Serological testing for TORCH infections should be performed (unless excluded in the mother in pregnancy):  
  a. in neonates with congenital microcephaly, or  
  b. where the head is disproportionately small relative to the face,  
    And  
  c. where Zika virus infection is suspected in the mother during pregnancy, or  
  d. any neurological signs or symptoms are present. |
| 9 | The role of serological and virological testing for Zika virus in neonates should be assessed based on further data on sensitivity and specificity and understanding of cross-reactivity with other flaviviruses. |
| 10 | Families of neonates with congenital Zika syndrome should be informed about the diagnosis, and advised regarding management and prognosis. |
| 11 | Psychosocial support and advice should be provided to families of neonates with congenital Zika virus syndrome as described in WHO interim guidance on 'Psychosocial support for pregnant women and for families with microcephaly and other neurological complications in the context of Zika virus'. |
| 12 | Infants with congenital Zika virus syndrome should receive a comprehensive neurodevelopmental assessment, and supportive therapy should be put in place for any difficulties noted, including irritability, seizures, swallowing difficulties, early onset spasticity and hip dysplasia. |
| 13 | Multidisciplinary approaches should be adopted to provide early interventions and support to promote neurodevelopment, prevent contractures and manage early complications as outlined in WHO mhGAP and community-based rehabilitation guidelines. |
| 14 | Infants with congenital Zika virus syndrome should be followed up at 1 month, 3 months, 6 months, 9 months, 12 months, 18 months and 24 months of age. Additional follow-up should be provided if there are other complications. Further follow-up beyond 24 months of age will be required depending on the child’s condition and needs. |
| 15 | At each visit, head circumference should be measured in order to monitor postnatal brain growth. For term newborns, WHO CGS for attained head circumference should be used to interpret the head circumference measurement. For preterm newborns, INTERGROWTH-21 preterm postnatal growth standards for attained head circumference should be used to interpret postnatal changes of head circumference until 64 weeks postmenstrual age. After this WHO CGS for attained head circumference should be used to interpret the head circumference measurement. |
| 16 | Developmental and neurological assessments should be performed with the full engagement of caregivers to identify developmental delays and other neurological abnormalities including epilepsy and disorders of movement, posture and swallowing. |
| 17 | Hearing should be screened in the first month of life as early as possible before discharge from hospital and further audiological evaluation and services should be provided as per the WHO guiding principles for newborn and infant hearing screening and the Position Statement from the Joint Committee on Infant Hearing. |
| 18 | There should be comprehensive ophthalmological assessment. |
| 19 | The health and well-being of the families and caregivers, including their psychological well-being should be assessed. |
| 20 | Infants born to mothers with suspected, probable or confirmed Zika virus infection during pregnancy, even without microcephaly or disproportionately small head relative to the face, should be followed up to detect, manage and investigate signs of neurodevelopmental abnormality including feeding difficulties, hearing or vision problems and poor head growth. Follow-up visits should occur at 3 months, 9 months and 24 months of age as a minimum. |
| 21 | Families and caregivers should be provided with psychosocial support and parenting advice. |

* Screening, assessment and management of neonates and infants with complications associated with Zika virus exposure in utero, WHO/ZIKV/MOC/16.3/Rev3, August 30 2016, World Health Organization*
Frequently asked questions (FAQ’s)

1. What is Zika virus?

Zika is a virus first isolated in Uganda in 1947. It is transmitted by the bite of infected mosquitoes identical to dengue. Although most patients have no symptoms, Zika may cause viral fever similar to dengue or chikungunya, with fever, skin rashes, body aches and headache. For further information on Zika, kindly refer to Info Sihat KKM.

2. What is microcephaly?

Microcephaly is a condition in which the size of the fetal head size is much smaller than usual for a baby of the same age, race, and sex.

There are multiple causes for microcephaly and it is not entirely related to infection. It can be caused by a variety of genetic and environmental factors, such as Down Syndrome, exposure to drugs, alcohol or other toxins in the womb; rubella and a few other infections during pregnancy.

Microcephaly may be picked up during pre-natal screening, such as through ultrasound of the fetus. However, not all cases may be picked up in the early stages of pregnancy (i.e. within the first trimester). Some may not be diagnosed until after late in the pregnancy or after the birth of the child.

There is no specific treatment for this condition. A significant proportion of fetuses with small heads on ultrasound turn out to be neuro-developmentally normal.

3. Is there any available test to confirm Zika infection?

Yes. Zika can be confirmed via reverse transcriptase-polymerase chain reaction (RT-PCR) test. It can be detected in the blood up to 7 days and up till 14 days in the urine from the onset of symptoms. These tests are readily available in almost all major governmental hospitals and IMR. The results take 2-4 working days.

However, the test is not accurate if performed beyond 14 days from the onset of symptoms and so it is not recommended if you are beyond 14 days or are asymptomatic.

4. If I am pregnant and asymptomatic, but worried about possible exposure to Zika should I go to get tested?

KKM Guideline does not recommend routine Zika testing for asymptomatic pregnant women. If you are concerned, you should discuss further with your doctor.
5. If I am pregnant and I have been in contact with someone who recently travelled to an area known to have Zika infection, do I have to be checked?

There is no need to see your doctor, if you are well. You should continue to take strict precautions against mosquito bites. If you have symptoms of possible Zika virus infection (fever and rash and other symptoms such as red eyes or joint pain), you should seek medical attention immediately.

6. Should a woman who is pregnant get regular blood/urine tests for Zika, to make sure that she is not infected?

No, unless she has symptoms of possible Zika Virus Infection (fever and rash and other symptoms such as red eyes or joint pain).

7. If I am pregnant and my male partner is tested positive for Zika, do I need to get tested if I do not have any symptoms?

If you have had sexual intercourse with your partner, you should consult a doctor and inform him/her of possible exposure to Zika.

8. Is it safe to use insect repellents in pregnancy?

Yes, insect repellents are safe in pregnancy. You can also prevent mosquito bites by wearing long, covered clothing, and sleeping under mosquito nets or in rooms with wire-mesh screens or air-conditioned rooms to keep out mosquitoes.

9. If a couple is planning for pregnancy and either one of them has been to a Zika endemic area, what precautionary measures should they take?

a) If both the man and woman are well
   They should take strict precautions against mosquito bites, and if they have further questions, consult their doctor.

b) If woman is symptomatic

   She should seek medical attention promptly, and if confirmed positive for Zika, she should practise safer sexual practices or abstain from sexual intercourse for at least 8 weeks after recovery, before trying to conceive.

c) If the man is symptomatic

   He should seek medical attention promptly, and if confirmed positive for Zika, he should practise safer sex through the correct and consistent use of condoms or abstain from sexual intercourse for at least six months after recovery.
10. How is my pregnancy management different in the context of Zika infection?

If you have symptoms suggestive of Zika with a recent history of travel to an area with Zika, you will be admitted to the hospital and will have blood and a urine test for confirmation. These tests will also be performed if you are within 14 days from the onset of symptoms.

However, if you are completely well without symptoms or are beyond 14 days from the onset of symptoms, confirmatory test are inaccurate and are not recommended.

If you screen positive for Zika, you will be managed by a specialist and will have 4 weekly ultrasound scans. You will be delivered in a specialist hospitals and your baby will be examined by a paediatrician after delivery.

11. If I get Zika infection in pregnancy, can I transmit the infection to my fetus and will my baby have microcephaly?

Yes, if you have Zika infection in pregnancy, it can be transmitted to the fetus. Although there is an association between Zika and the risk of microcephaly, it is difficult to estimate the absolute risk which may be high during outbreaks. The risk is highest if you get infected before 28 weeks of pregnancy.

12. Can mothers with Zika infection breastfeed their baby?

Zika virus has been detected in breast milk but there is currently no evidence that the virus is transmitted to babies through breastfeeding.

13. What are the important precautionary methods to reduce my risk of Zika infection?

The most essential preventive measure is prevention of mosquito bites. The Aedes mosquito is easily identifiable by the distinctive black and white stripes on its body. It prefers to breed in clean, stagnant water easily found in homes. It is important to frequently check and remove stagnant water.

Pregnant women should postpone non-essential travel to countries with ongoing outbreaks. Travellers to countries with local transmission of Zika virus should protect themselves from mosquito bites by wearing long, covered clothing, applying insect-repellent, and sleeping under mosquito nets or in rooms with wire-mesh screens to keep out mosquitoes. They should seek medical attention promptly if they become unwell.

All travellers returning from areas with ongoing outbreaks of Zika should adopt safer sexual practices, e.g. consistent and correct use of condoms during sex, or consider abstinence for at least eight weeks after their return. Male travellers who are symptomatic should adopt safer sex practices or consider abstinence for at least 6 months.
Travellers who have returned from Zika affected areas should monitor their health for the next 14 days and consult a doctor if they have symptoms of Zika, such as fever, skin rashes, joint and muscle pains, headaches and red eyes. They should inform the doctor of the areas that they have travelled to.
Guideline on the Management Zika Virus-Related Guillain-Barré Syndrome (GBS)

The Guillain-Barré Syndrome (GBS) is an acute monophasic illness causing a rapidly progressive polyneuropathy with weakness or paralysis.

1. Clinical presentation

Progressive, mostly symmetrical ascending muscle weakness and absent or depressed deep tendon reflexes. Additional neurological features include facial, oculomotor, respiratory, and bulbar muscles weakness. In some cases, dysautonomia may occur. In case of severe respiratory muscle weakness developed, intensive care and mechanical ventilatory support may be required. GBS usually progresses over a period of about two weeks.

Majority of the reported Zika virus-related GBS syndrome did not differ in terms of clinical presentation compared with the typical GBS. A significant proportion of them are experience transient illness including rash (>80%), arthralgia (>70%) and fever (>50%) in a median of 6 days before the onset of GBS symptoms. In addition to the typical GBS features of muscle weakness, areflexia or decreased reflexes, up to 60% of patients with Zika virus-related GBS develop facial palsy either unilateral or bilateral. On electrophysiology study, patients with Zika virus-related GBS demonstrated 'reversible conduction failure' (RCF) consistent with Acute Motor Axonal Neuropathy (AMAN) subtype. However, early electrophysiology features (prolonged distal latencies and reduced distal CMAP) in this GBS subtype may be misinterpreted as acute demyelinating neuropathy. Cerebrospinal fluid (CSF) analysis may show evidence of cytoalbuminologic dissociation. However, anti-gangliosides antibodies are typically negative.

2. Diagnosis

Initial diagnosis of GBS is based upon the clinical presentation. This is supported by cerebrospinal fluid (CSF) analysis, anti-gangliosides antibody and clinical neurophysiology studies. The World Health
Organization (WHO) recommends use of the **Brighton criteria for the case definition of GBS** in regions affected by Zika virus transmission. Zika virus testing should be done in all patients suspected with GBS, if and where these diagnostic facilities are available.

3. **Management**

There is no specific management available for Zika-related GBS to-date. Once a diagnosis of GBS is made, close monitoring and initial supportive care are extremely important in the management. This is to identify those with GBS who might progress to develop respiratory failure requiring mechanical ventilation. In addition, severe autonomic dysfunction may occur and warrants intensive care unit (ICU) monitoring. Parameters that need intensive and frequent monitoring include forced vital capacity, oxygen saturation, cardiac and blood pressure monitoring.

For severe cases, the main treatment options for GBS are intravenous immunoglobulin (IVIG) or plasma exchange (PLEX). Both the treatments improve outcome and are equivalent. Treatment options are based on clinician's experience, local availability as well as patient's associated risk factors. There is no evidence at present, to support the use of steroids in the treatment of GBS.

Treatment of GBS is best managed through a multidisciplinary team. In addition to IVIG or PLEX treatment, patient should be seen early by physiotherapist and rehabilitation physician. Occupational therapist and speech therapist assessment should be referred accordingly depending on the clinical presentation and extent of neurological involvement.
ALGORITHM FOR ZIKA-RELATED GBS MANAGEMENT

**Symptoms & signs:** (Combination of followings)
- Paraesthesia of limb extremities followed by evolving ascending muscle weakness
- Absent / depressed deep tendon reflexes (DTRs)
- *Bilateral asymmetrical facial palsy +/- ocular, bulbar, respiratory muscle weakness*
- *Dysautonomia e.g. Cardiac arrhythmias, orthostatic hypotension* WITH preceded rash (usually pruritic and maculopapular) and two or more of the following symptoms:
  - Fever, arthralgia, arthritis/periarticular oedema or conjunctivitis (Non-purulent/hyperaemia)

Apply the **Brighton criteria for case definitions of GBS:** (see Appendix 1)

Optional investigations depending on local availability:
- CSF examination (cytoalbuminologic dissociation<50 cells/μL)
- Nerve Conduction Study (Consistent with axonal (RCF) subtype GBS)
- Serum Anti-Gangliosides study (to be sent to IMR)

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**Diagnosis of GBS**

Zika virus RT-PCR (Blood, Urine, CSF)

Negative

Positive

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Notify Pejabat Kesihatan Daerah (PKD) with form Zika1/case/2016

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Monitor bulbar, respiratory function, BP & FVC

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**Stable AND walks** unassisted, minimal neurological deficit with no progression

**Stable BUT walks assisted** /bedbound & progressive disease

**Unstable** Refer to ICU for mechanical ventilation

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Conservative & supportive management

IVIG / PLEX & supportive management

IVIG / PLEX & supportive management
Appendix 1: Brighton Criteria for Case Definition of Guillain-Barré Syndrome

<table>
<thead>
<tr>
<th>Level 1 of diagnostic certainty</th>
<th>Level 2 of diagnostic certainty</th>
<th>Level 3 of diagnostic certainty</th>
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<tr>
<td>• Bilateral and flaccid weakness of the limbs; <strong>AND</strong></td>
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<td>• Bilateral and flaccid weakness of the limbs; <strong>AND</strong></td>
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<tr>
<td>• Decreased or absent deep tendon reflexes in weak limbs; <strong>AND</strong></td>
<td>• Decreased or absent deep tendon reflexes in weak limbs; <strong>AND</strong></td>
<td>• Decreased or absent deep tendon reflexes in weak limbs; <strong>AND</strong></td>
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<tr>
<td>• Monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; and subsequent clinical plateau; <strong>AND</strong></td>
<td>• Monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; and subsequent clinical plateau; <strong>AND</strong></td>
<td>• Monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; and subsequent clinical plateau; <strong>AND</strong></td>
</tr>
<tr>
<td>• Absence of identified alternative diagnosis for weakness; <strong>AND</strong></td>
<td>• Absence of identified alternative diagnosis for weakness; <strong>AND</strong></td>
<td>• Absence of identified alternative diagnosis for weakness; <strong>AND</strong></td>
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<td>• Cytoalbuminologic dissociation (i.e.: elevation of CSF protein level above laboratory normal value and CSF total white cell count &lt;50 cells/microL; <strong>AND</strong></td>
<td>• CSF total white cell count &lt;50 cells/microL (with or without CSF protein elevation above laboratory normal value); <strong>OR</strong></td>
<td>• Electrophysiologic studies consistent with GBS if CSF not collected or results not available</td>
</tr>
<tr>
<td>• Electrophysiologic findings consistent with GBS</td>
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</tbody>
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References:

5. Kornberg, AJ, for the Asia–Pacific IVIg Advisory Board 2004, Bringing consensus to the use of IVIg in neurology. Expert consensus statements on the use of IVIg in neurology, 1st edn, Asia–Pacific IVIg Advisory Board, Melbourne, pp. 14–20
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