# Pregnancy management in the context of Zika virus infection

## Interim guidance update

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## 1. Introduction

### 1.1 Background

Zika virus is a flavivirus that is primarily transmitted by infected *Aedes* mosquitoes. This vector also transmits dengue and chikungunya viruses and is commonly found in tropical and sub-tropical environments in Africa, the Americas, Asia and the Pacific. Although Zika virus was first identified in humans in 1952, few outbreaks were documented prior to 2015.(1) Human infection can be asymptomatic, and when there are symptoms, these are usually mild and self-limiting. While the usual pattern of human infection has not changed, the recent potential association between Zika virus infection and congenital microcephaly and Guillain-Barré syndrome in some affected areas(2) has escalated this issue to a Public Health Emergency of International Concern.(2-4)

Although Zika virus infection in pregnancy is typically a mild disease, an unusual increase in cases of congenital microcephaly and other neurological complications in areas where outbreaks have occurred(2, 3) has significantly raised concern for pregnant women and their families, as well as among health providers and policy-makers.(5)

The association between Zika virus infection and fetal malformations is still being investigated,(6) however there is increasing evidence that maternal-fetal transmission of Zika virus can occur throughout pregnancy.(7-9) Laboratory isolation of the virus in the neurologic tissues of infants with microcephaly has further added to the suspicion of a causal relationship.(9) It is also unclear whether Zika virus infection contributes to spontaneous pregnancy losses and stillbirths,(10, 11) although Zika virus RNA has been detected in products of conception following miscarriage by infected women.(12) Rapidly accumulating evidence from the current outbreak appears to support a link between Zika virus infection and microcephaly and other serious brain abnormalities.(13, 14)

### 1.2 Rationale and objectives

The purpose of this document is to update information and recommendations provided in the WHO interim guidance on *Pregnancy management in the context of Zika virus*, published on 2 March 2016. This update includes narrative summaries of evidence that underlie the recommendations for practice, and a section on antenatal testing and care for pregnant women with a history of travel to areas of active Zika virus transmission.

This guidance is intended to inform the development of national and local clinical protocols and health policies that relate to pregnancy care in the context of Zika virus transmission. It is not intended to provide a comprehensive practical guide for the prevention and management of maternal Zika virus infections.

### 1.3 Scope of the guidance

The guidance is relevant to all pregnant women residing in areas of Zika virus transmission, particularly for pregnant women suspected of being at risk of, or diagnosed with Zika virus infection. It is also applicable to pregnant women with possible Zika virus exposure through travel to an area with active Zika virus transmission or unprotected sexual contact with an infected partner. It does not cover non-pregnant women, or the management and follow-up of newborns.

### 1.4 Target audience

The primary audience for this guidance includes health professionals who are directly providing care to pregnant women including general practitioners, obstetricians, midwives and nurses. The guidance may also be used by those responsible for developing national and local health protocols and policies, as well as managers of maternal and child health programmes, especially in regions with unusual increases in adverse fetal and newborn outcomes suspected to be associated with Zika virus infection.

## 2. Methods

This guidance builds on existing recommendations from WHO and other international agencies. The guidance development process consisted of: identification of priority questions; rapid literature search and retrieval of evidence; assessment and synthesis of available evidence; and formulation of recommendations.

### 2.1 Evidence retrieval, assessment and synthesis

Using a list of key questions and outcomes prioritized from a previous scoping exercise, a WHO steering group, along with the systematic review teams, searched for relevant or potentially relevant individual studies and systematic reviews. Where there was no existing systematic review for a specific question, a new systematic review was conducted. To identify relevant studies, systematic searches of various electronic sources were conducted including MEDLINE, EMBASE, CENTRAL, CINAHL, POPLINE, NLM Gateway and WHO Global Health Library and regional databases. The search strategies employed to identify the studies and the specific criteria for inclusion and exclusion of studies are described in the individual systematic reviews. Studies were considered for inclusion, irrespective of date, language or study location.

The scientific evidence underpinning the clinical recommendations was synthesized from individual studies or existing and new systematic reviews by the systematic review teams in conjunction with the WHO steering group. No formal grading of the quality of evidence was performed.

### 2.2 Formulation of recommendations

The WHO steering group used the available evidence and expert consultations to draft clinical recommendations and a decision-chart for testing and care of pregnant women in the context of Zika virus infection. WHO convened two technical consultations of an international group of experts – the guideline development group (GDG) – on 16 February and 17-19 March 2016, where the GDG reviewed and approved the recommendations based on the synthesized evidence and expert opinion.

To formulate the recommendations, the GDG considered available evidence, the balance of desirable and undesirable effects of the interventions, the values and preferences of persons affected by the guidance, feasibility and resource implications for health systems in different settings. Before publication, the draft guidance was peer-reviewed to identify any factual errors and to provide comments on the clarity of the language, contextual issues and implications for implementation.

## 3. Evidence and recommended practices

Sections 3.1 to 3.6 contain summaries of evidence for key questions (in blue boxes) followed by the corresponding recommendations for practice. The recommendations cover practices related to the prevention of maternal Zika virus infection; clinical presentation and diagnosis of Zika virus infection; general care and symptomatic treatment; and antenatal tests, evaluation and care of pregnant women possibly exposed to Zika virus infection.

### 3.1 Preventive measures

*Summary of evidence*

*Vector control interventions*: Interruption of human-to-vector contact has been widely advocated as the most effective measure to prevent or reduce the risk of transmission of vector-borne viruses. Although the systematic review did not identify direct evidence on the impact and safety of vector control interventions for Zika virus infection, there is indirect evidence from studies relating to other viral infections (e.g. dengue) that share the same *Aedes* mosquito vector with Zika virus.

A systematic review of randomized and non-randomized studies evaluating the effectiveness of vector control interventions in reducing human dengue virus infection and markers of *Aedes aegypti* density identified 41 relevant studies (with 19 providing data for meta-analysis).(15) The review considered both individual-level and environmental interventions, used either singly or in combinations and was not specific to pregnant women. The use of screens in homes significantly reduced dengue incidence compared to homes without screens (odds ratio [OR]) 0.22, 95% CI 0.05-0.93). Community-based environmental management combined with the use of covers for water containers reduced dengue infection (OR 0.22, 95% CI 0.15-0.32). Indoor residual spraying, insect repellents, bed nets, mosquito nets and traps did not impact dengue infection risk while insecticide aerosols and mosquito coils were associated with higher dengue risk. Overall, there is little evidence from appropriately designed trials to draw conclusions on the effectiveness of any particular vector control intervention in reducing dengue infection. However, there is evidence that community-based combination interventions (e.g. waste disposal, clean up campaigns and formation of community working groups) are effective in reducing markers of *Aedes aegypti* density.

*Efficacy and safety of insect repellents*: A systematic review reports that DEET (N, N-diethyl-3-methylbenz-amide), Icaridin and Insect Repellent (IR) 3535 (ethyl-butylacetyl-amino-propionat, EBAAP) are effective in reducing mosquito bites with variations in mean complete protection time according to the concentration of the active agent.(16) Animal model studies (n=7) on Deltametrin, Icaridin, DEET, Permethrin and Citriodora showed no side effects in pregnant rats, mice or rabbits and their offspring. Four studies in pregnant women examined the use of Permethrin in nets for preventing malaria and for treatment of head lice and scabies and concluded that it is safe for use during pregnancy. One double-blind, randomized trial of insect repellents for the prevention of malaria in pregnancy (n=897) showed that daily application of DEET (1.7 g/day) in the second and third trimesters showed no adverse effects on survival or growth and development at birth and at one year of age.(17) Although the published literature on safety of IR3535 during pregnancy is sparse, this repellent was deemed safe by WHO in 2006 and 2011 based on unpublished data provided by the manufacturer.

*Potential sexual transmission*: A review of the literature identified six reports demonstrating the possibility of sexual transmission of Zika virus.(18-23) All reported presumed sexual transmission through unprotected sexual intercourse with a male partner who had a history of symptoms consistent with Zika virus infection. No report was found on sexual transmission from a woman to a man or from an infected but asymptomatic man to a woman. The duration of Zika virus persistence in semen was generally not well investigated in these reports. However, in two of the reports, high viral load

and replicative Zika virus particles were detected in semen samples more than two weeks after onset of symptoms, but the virus was undetectable by reverse transcription polymerase chain reaction (RT-PCR) in blood samples collected at the same time.(21, 22) In another report, Zika virus particles were detected by RT-PCR at 27 and 62 days after onset of a febrile illness, suggesting a prolonged potential for sexual transmission.(23)

### 3.1.1 Vector control and personal protection

It is essential to correct the social determinants of viral illnesses that are transmitted by *Aedes aegypti* mosquitoes at the population level. Strategies to considerably reduce the potential threat of Zika virus infection should therefore include concerted efforts to provide sustainable and equitable access to safe and clean water; consistent application of sanitation and hygiene practices; and appropriate waste management at the community level.

Infection prevention measures for pregnant women are the same as those recommended for the general population. However, the importance of preventive measures should be emphasized at every contact with a pregnant woman. Health care professionals should promote the following measures with pregnant women and their families, and in the community.

**Vector control**: Environmental measures should be undertaken to reduce vector density. As mosquito control is the only measure that can successfully interrupt transmission of viruses such as Zika, dengue, and chikungunya, every effort should be made to identify and destroy potential mosquito breeding sites from homes and workplaces.[a]

- Pregnant women, their family members and pregnancy-related community groups should be advised to actively engage with neighbourhood efforts to reduce breeding sites of vectors, with use of larvicides where appropriate.

**Personal protection measures**: The following interventions are recommended for the general population and for pregnant women in particular:

- Protection of the skin from exposure to mosquitoes by wearing clothes that cover as much of the body as possible (e.g. long sleeves, long trousers or skirts). Based on entomological studies, the use of light coloured clothes is preferred.
- Use of mosquito bed nets (insecticide treated or not), including when sleeping during the daytime.
- Use of mosquito mesh/nets/screens (insecticide treated or not) on windows and doors.
- Use of insect repellents approved by local health authorities for safe use in pregnancy (e.g. DEET-based repellents). Repellent should be applied as required on exposed body areas and even over clothes, and re-applied as indicated by the manufacturer on the product label to ensure complete protection.
- Use of the above personal protection measures by individuals infected with Zika, dengue, and or chikungunya viruses should be encouraged to avoid the spread of infection to uninfected individuals. These measures should be implemented at least during the first week of onset of symptoms (viraemic phase).
- To prevent potential sexual transmission of Zika virus, sexual partners of pregnant women, living in or returning from areas of ongoing Zika virus transmission, should correctly and consistently use latex condoms for sexual activity for the duration of the pregnancy.[b]

## 3.2 Diagnosis

*Summary of evidence*

*Clinical manifestations*: A systematic review of evidence on the characteristics of Zika virus infection in pregnant women identified five cohort studies and 13 case reports.(24) However, these studies had significant limitations as ascertainment of clinical characteristics was largely made retrospectively and laboratory confirmation of suspected cases was often incomplete. The review showed that there is no evidence to suggest increased susceptibility to infection in pregnant women compared with nonpregnant or general populations.

Pregnant women with confirmed Zika virus infection were commonly reported to have developed a rash, fever, conjunctivitis, and arthralgia. Currently available data did not allow evaluation of variation in clinical manifestation of infection based on factors such as gestational age at the time of infection, level of viraemia, coinfection with other flaviviruses, parity, or socioeconomic factors. However, the clinical symptoms and signs reported in pregnant women were consistent with those described for general populations – rash, fever, arthritis or arthralgia, and conjunctivitis. Other less common symptoms included myalgia, headache, retro-orbital pain, oedema, and vomiting. A prospective cohort study describing the clinical presentation of pregnant women presenting with any kind of rash reported that the predominant clinical features of maternal Zika virus infection included pruritic descending macular or maculopapular rash, arthralgia, conjunctival injection, and headache. Only 28% of women had a short-term, low-grade fever.(11) Compared with women without Zika virus infection, the rash in women with Zika virus infection was more likely to be maculopapular, and conjunctival injection and lymphadenopathy (isolated or generalized) were also more frequent. In the same study, the rash persisted between 2 and 14 days (median, 4 days).

The symptoms reported were generally mild and self-limiting. None of the studies reported haemorrhagic complications or a maternal death. One study reported a case of a pregnant

[a] Additional information on vector control can be found at http://www.who.int/mediacentre/factsheets/zika/en/

[b] Additional information on prevention of potential sexual transmission can be found at http://www.who.int/csr/resources/publications/zika/sexual-transmission-prevention/en/

woman with Guillain-Barré syndrome but there were no other reports of severe maternal morbidity. In general, most of these studies were biased by including mainly women with suspected Zika virus disease and thus precluding a clear understanding of the proportion of infected women who do not present with symptoms. Data from the general population in a previous outbreak in Yap, Federated States of Micronesia, suggested that Zika virus infection was symptomatic in approximately one out of every five infected people.(25)

*Laboratory diagnosis*: Available studies suggest similarity in the laboratory protocol for viral detection and assessment of serologic parameters of the immune response. Reports from previous and current outbreaks showed that laboratory analysis and case confirmation of individuals with symptoms were based on the results of RT-PCR) testing of whole blood (or serum or plasma) samples during the acute phase or presence of IgM antibodies against Zika virus during the convalescent phase.(25-27) Studies have shown that RT-PCR detection of the virus in maternal serum was confined to 5-7 days after onset of symptoms. Zika virus RNA has also been detected in urine with the period of shedding lasting up to three weeks after the onset of symptoms (28, 29) and in saliva although the period of virus shedding appears to be the same as in serum.(30) RT-PCR has also been used to identify Zika viral RNA in fluid obtained through amniocentesis and in histopathologic tissues from autopsy specimens.(8, 31) Evidence is lacking on the diagnostic accuracy of RT-PCR testing of amniotic fluid for detecting congenital Zika virus infection, and on the optimal time to perform amniocentesis.

### 3.2.1 Clinical manifestations

There is currently no known difference between the clinical manifestations of Zika virus-infected pregnant and non-pregnant women. Zika virus infection may be symptomatic or asymptomatic. In symptomatic cases, symptoms typically appear a few days after the bite of an infected mosquito. Most symptomatic pregnant women will get a rash, which is often maculopapular and pruritic. Others may also get fever, conjunctivitis, joint pain, headache, muscle pain, and feel tired. These symptoms last 2–7 days and are generally mild and self-limiting. In some cases, the rash may persist for up to 14 days.

Some countries with active Zika virus transmission have reported an increased occurrence of neurological syndromes, including, but not limited to Guillain-Barré syndrome. Guillain-Barré syndrome is a condition that can occur during pregnancy. Therefore, it is important to investigate for Zika virus infection in any pregnant woman presenting with Guillain-Barré syndrome or other neurological complications in the context of Zika virus transmission.

**Case definition of Zika virus disease:** Interim case definitions for Zika virus disease have been developed by WHO and can be accessed at http://www.who.int/csr/disease/zika/case-definition/en.

### 3.2.2 Laboratory diagnosis

The diagnostic steps recommended for pregnant women are the same as those recommended for the general population.[c] Diagnosis requires detection of the virus in maternal serum using RT-PCR) within seven days of onset of symptoms. Zika virus may also be detected in urine specimens collected in the acute phase of the illness and up to three weeks after the onset of symptoms. RT-PCR can also be used to identify viral RNA in saliva and amniotic fluid, but these should not be used as the primary specimens for Zika virus testing.

Serological tests can also be performed to diagnose Zika virus infection with IgM antibodies detected through enzyme linked immunosorbent assays (ELISA) or immunofluorescence from the seventh day following onset of symptoms. Following an individual's first infection with a flavivirus, cross reactions with other genetically related viruses in serological tests are minimal. However, the serum of individuals with a previous history of infection by other flaviviruses has an increased likelihood of cross reaction. Considering that a substantial proportion of the population living in areas with ongoing Zika virus transmission can be assumed to have had previous contact with other flaviviruses (especially dengue and yellow fever, including yellow fever vaccine), cross-reactions and false positive results are possible. Careful attention should be given to ensure that any serological test that is used to guide the management of pregnancy has been validated by a competent national or international authority.

## 3.3 General care and symptomatic treatment

*Summary of evidence*

*Treatment options*: Available data from a systematic review shows that the natural history of Zika virus infection is still poorly understood and consequently there is a lack of effective treatment options.(24) Current evidence suggests a generally mild and self-limiting disease in those with symptoms. Where reported, treatment has been limited to general care for viral infections and care for specific symptoms in infected individuals. To date, no vaccine, antiviral agent or specific therapy has been developed for Zika virus infection to reduce the clinical impact or risk of fetal infection. Consequently, treatment has focused on interventions that can be safely used in pregnant women to relieve an itchy rash, fever, headache, and arthralgia.

*Effectiveness and safety of topical emollients and antihistamines*: A 2016 Cochrane systematic review evaluated pharmacological interventions for treating generalized itching not due to systemic disease.(32) The review considered all published, unpublished and ongoing randomized controlled trials evaluating topical agents (phenol, menthol and camphor; topical anaesthetics, steroids, capsaicin) and systemic drugs (antihistamines, aspirin, steroids, opioid antagonists, and

[c] Additional information on laboratory testing for Zika virus infection can be found at http://www.who.int/csr/resources/publications/zika/laboratory-testing/en/

antidepressants). The review did not identify any eligible trials. No other systematic reviews evaluating safety and effectiveness of pharmacological interventions to relieve itching during pregnancy were identified.

Regarding safety, various studies on the use of antihistamines (H1 blockers) during pregnancy have shown no increase in adverse fetal outcomes, especially with respect to teratogenicity. One systematic review of observational studies evaluating the risk of major malformations associated with first trimester exposure to antihistamines (H1 blocker) with data for over 200,000 pregnancies showed no increase in teratogenicity (summary OR 0.76 (95% Cl: 0.60-0.94).(33)

A systematic review evaluating an association between prenatal exposure to antihistamines and birth defects included 54 observational studies (31 cohort and 23 case-control studies).(34) The majority of women in the studies were from Canada, Scandinavia and the United States of America. The studies included first generation H1-receptor antagonists (cyclizine or meclizine, doxylamine plus pyridoxine, hydroxyzine, brompheniramine, chlorpheniramine, diphenhydramine, promethazine, and triprolidine) and second generation H1-receptor antagonists (cetirizine, loratadine, terfenadine and astemizole). The review concluded that the safety of antihistamine use during pregnancy with respect to birth defects is generally reassuring, although one large study from Sweden in 2002 suggested an association between loratadine and hypospadias, warranting a detailed evaluation in other populations. Later studies, however, did not support this association.

### 3.3.1 Rest and use of personal protection measures

Symptomatic pregnant women with Zika virus infection should be advised to rest and use the personal protection measures described in section 3.1.1 to reduce the likelihood of viral transmission to other people, particularly during the first week of the disease (viraemic phase).

### 3.3.2 Fever and headache

Fever should be managed with physical cooling measures (e.g. damp cloths, light clothing, baths or showers) and acetaminophen (paracetamol). The use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAID) should be avoided until dengue viral infection has been excluded. Headache should also be treated with paracetamol (acetaminophen) at the dosages prescribed for fever management.

### 3.3.3 Itchy rash

Although there is no evidence to either support or refute the safety of topical emollients for treatment of itchy rash during pregnancy, clinical experience suggests that they are safe. Therefore, topical applications of calamine lotion or menthol-based aqueous agents may be used.

In general, the safety profile of most antihistamines for systemic treatment of itching during pregnancy is high. However, if a pregnant woman with Zika virus infection strongly wishes to use antihistamines to relieve itching due to a rash, an oral first generation antihistamine, usually chlorpheniramine, is recommended as a first line treatment. Loratadine and cetirizine should be provided as alternative options after the first trimester of pregnancy.

## 3.4 Antenatal tests for pregnant women living in/with a history of travel to areas with ongoing Zika virus transmission

*Summary of evidence*

*Universal versus targeted Zika virus testing*: Review of the literature found no studies comparing the effectiveness of universal versus targeted Zika virus infection testing of pregnant women or any population. While universal testing of all pregnant women in the affected area may help identify asymptomatic but infected pregnant women who may potentially be at increased risk of fetal malformation, it does not meet the classic Wilson and Jungner criteria endorsed by WHO for a useful screening test.(35) Due to the considerable evidence gap regarding Zika virus disease progression and effective treatment or interventions, the following components of the Wilson and Jungner screening criteria are not met: there should be an accepted treatment for patients with recognized disease; facilities for diagnosis and treatment should be available; the natural history of the condition, including development from latent to declared disease, should be adequately understood; and the cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole (cost-effectiveness).(35) Consumer-generated demands for screening tests that do not meet these stringent criteria have been shown to result in expensive programmes of no clear value.

In addition, the diagnostic accuracy of available serologic tests in identifying infection in apparently healthy populations is unknown, especially in affected areas where cross-reactions between Zika and other flaviviruses are common. Evidence is sparse on the level of risk (or incidence) of Zika virus infection in asymptomatic pregnant women residing in infected areas or those potentially exposed through travel or sexual contact.(24) This makes it challenging to estimate the positive and negative predictive values of any screening test. Estimation through modelling of data from a previous outbreak indicated that 0.95% of infected mothers gave birth to babies with microcephaly(36) suggesting that the proportion of false positives may be very high. During the current outbreak, one cohort study in Brazil showed that 72 (82%) of 88 pregnant women presenting to a clinic with a rash in the previous five days tested positive for Zika virus with RT-PCR,(11) suggesting that the occurrence of rash can be used to identify women at higher risk of having the infection during an outbreak and who require further diagnostic testing for case confirmation.

*Routine ultrasound in early pregnancy*: Evidence on the usefulness of routine fetal ultrasound in early pregnancy for diagnosing fetal malformation was extracted from a Cochrane review.(37) The review compared routine with selective ultrasound examinations in pregnancies less than 24 weeks for detection of fetal malformations, multiple pregnancies, and incidence of adverse fetal outcomes. There is evidence that routine ultrasound scans improved detection of major fetal abnormalities before 24 weeks'

gestation (relative risk [RR] 3.46, 95% CI 1.67 to 7.14). Routine ultrasound in early pregnancy also improved gestational age dating, as it was associated with a reduction in labour inductions for 'post term' pregnancy (RR 0.59, 95% CI 0.42 to 0.83). However, there was low quality evidence that it did not influence the risk of perinatal death (RR 0.89, 95% CI 0.70 to 1.12).

*Amniocentesis for prenatal diagnosis of Zika virus fetal infection*: There are a number of reports showing that Zika virus RNA can be isolated from the amniotic fluid of pregnant women with or without positive serological tests for Zika virus.(7, 31) However, there is currently no evidence on the diagnostic accuracy of the RT-PCR test in identifying congenital infection, and to what extent a positive test is predictive of subsequent fetal malformation. There is also no evidence on the optimal time to perform the procedure to diagnose congenital Zika virus infection.

Regarding safety of amniocentesis, evidence was extracted from a Cochrane review evaluating the comparative safety and accuracy of early (< 15 weeks) and second trimester amniocentesis (>15 weeks), and chorionic villus sampling techniques for prenatal diagnosis.(38) The review showed that compared to no amniocentesis, second trimester amniocentesis resulted in an increased risk of spontaneous miscarriage of 0.8% (RR 1.60; 95% CI 1.02 to 2.52). There was no difference in vaginal bleeding between the groups, but amniotic fluid leakage was more common after amniocentesis (RR 3.90, 95% CI 1.95 to 7.80). Compared to an early amniocentesis, second-trimester amniocentesis is safer and technically less demanding. Total pregnancy loss after early amniocentesis was significantly higher (RR 1.29; 95% CI 1.03 to 1.61) and the number of congenital anomalies was also significantly increased in the early amniocentesis group.

### 3.4.1 Zika virus testing and ultrasound assessments

Testing for Zika virus infection is currently recommended for pregnant women presenting with a history of Zika virus disease symptoms or signs. WHO does not, at this time, recommend testing all pregnant women living in (or with a history of travel to) areas of ongoing Zika virus transmission. However where possible, health professionals should consider offering a first trimester ultrasound scan to all women presenting for antenatal care in order to accurately date the pregnancy and perform a basic fetal morphology assessment.

**Annex 1** provides a decision-chart for the testing and care of pregnant women living in areas with ongoing Zika virus transmission. All pregnant women should be advised to present for their scheduled antenatal visits in accordance with national standards and to comply with the recommendations of their health care providers. At each visit, women should be asked about the occurrence of any of the symptoms or signs of Zika virus infection, since their last antenatal visit. If it is their first antenatal contact, they should be questioned about the occurrence of these symptoms during the current pregnancy. Women should be counselled to present early for diagnostic work up and treatment if they develop any of these symptoms in between scheduled antenatal visits. During all antenatal visits, all women should be provided with information on standard environmental and individual protection measures as described in section 3.1.1.

Regardless of a history of illness consistent with Zika virus infection, all women in areas of ongoing Zika virus transmission should be requested to have a fetal anomaly scan between 18 and 20 weeks or at the earliest possible time if the first visit occurs after 20 weeks. Careful attention should be paid to the fetal central nervous system to identify any abnormalities, including microcephaly and other intracranial structural deformities.

Women with a history of clinical illness who test negative for Zika virus infection but who have no evidence of fetal brain abnormalities/other abnormalities on ultrasound, should continue to receive routine antenatal care. A repeat fetal ultrasound in late second or early third trimester, preferably between 28 and 30 weeks of gestation, is recommended to identify fetal microcephaly and/or other brain abnormalities when they are much easier to detect. This is because it is possible for the mother to be infected and for the fetus to be affected after an initial negative Zika virus test and a normal ultrasound examination.

**Annex 2** provides a decision-chart for the testing and care of pregnant women who do not reside in areas with ongoing Zika virus transmission, but who have a history of travel to such areas while pregnant. Health providers should carefully assess the woman's travel history based on the most recent update provided by the WHO.[d] The recommendations for antenatal tests, evaluation and care are essentially similar to those for women living in areas with ongoing Zika virus transmission.

### 3.4.2 Amniocentesis

Amniocentesis is an invasive procedure that should be reserved for specialized obstetric care and settings. Where feasible, and with full discussion of the potential risks with the pregnant woman, amniocentesis could be considered for women with negative Zika virus test results but abnormal fetal brain ultrasound findings, to screen for genetic abnormalities and congenital infections including Zika virus. It should be noted that the diagnostic accuracy of RT-PCR testing of amniotic fluid to detect congenital Zika virus infection is currently uncertain, and it is unknown if a positive test result is predictive of subsequent fetal malformation. When indicated, the procedure should be performed

[d] Zika virus situation report can be found at http://www.who.int/emergencies/zika-virus/situation-report/en/

after 15 weeks of gestation and only when the risks and benefits of the procedure have been well discussed and are acceptable to the pregnant woman.

## 3.5 Antenatal evaluation of Zika virus-related fetal brain/ other abnormalities

*Summary of evidence*

*Fetal abnormalities presumably associated with Zika virus infection*: A systematic review evaluating the spectrum of fetal abnormalities presumably associated with Zika virus infection identified five cohort studies and 13 case reports reporting on a wide spectrum of abnormal findings on fetal ultrasound.(24) The most common of these features include microcephaly, intracranial calcifications, and ocular lesions or calcifications. Others include ventriculomegaly, abnormal sulcation and gyration, abnormal cortical development (lissencephaly) cerebral atrophy, callosal dysgenesis, failure to visualize different portions of the brain, cerebellar abnormalities including atrophy, brainstem hypoplasia, microophthalmia, and arthrogryposis. There are also reports of intrauterine growth restriction, evidence of placental insufficiency, and intrauterine fetal death.

*Diagnostic accuracy of fetal ultrasound diagnosis of microcephaly*: Evidence was extracted from a systematic review examining the diagnostic accuracy of measurements of fetal dimensions compared with reference measurements at birth for prenatal diagnosis of microcephaly.(39) Participants in the review included pregnant women for whom prenatal ultrasound assessments for microcephaly were conducted and confirmed during the postnatal period (with a plan to conduct a subgroup analysis for Zika virus-infected pregnant women). The review found nine studies conducted in hospital settings in the United States of America (5), Canada (1), France (1), and Israel (2) using a single parameter or a combination of parameters as an index test for diagnosing microcephaly. These include abdominal circumference, biparietal diameter, femur length, head circumference (HC), and occipito-frontal diameter (OFD). The studies commonly assessed the accuracies of the index tests using different thresholds (1, 2, 3, 4, and 5 standard deviations (SD) below the mean for gestational age or the 5th centile).

Two studies (involving 45 fetuses) used OFD as an index test. Using a threshold of 3, 4 and 5 SD below the mean, meta-analysis of the results showed sensitivities of 76%, 58%, and 58%; and specificities of 84%, 97% and 97%, respectively. Both studies also used HC as an index test. At the same thresholds of 3, 4 and 5 SD < mean, meta-analysis of the results showed sensitivities of 84%, 68%, and 58%; and specificities of 70%, 91% and 97%, respectively. Using model-based data of 95 cases of microcephaly per 10,000 women with infection,(36) the positive predictive values were extremely low while negative predictive values were very high across 3, 4, and 5 SD < mean thresholds for both OFD and HC parameters. For both index parameters, the diagnostic odds ratios were statistically significant and increased considerably as the standard deviations below the mean increased.

The review concluded that fetal ultrasound seems better at accurately defining the absence of microcephaly than its presence. Compared to the other parameters reported, OFD and HC were more consistent in specificity and sensitivity across studies and at lower thresholds compared to higher thresholds.

### 3.5.1 Spectrum of abnormal fetal ultrasound findings

In the context of Zika virus transmission, ultrasound examination should be directed at identifying fetal brain/ other abnormalities including microcephaly, ventriculomegaly, intracranial calcifications, abnormal sulcation and gyration, brain atrophy, callosal dysgenesis, microophthalmia, and eye calcifications which have been reported in affected pregnancies.(8) Ultrasound findings of abnormalities of amniotic fluid, intrauterine growth restriction or fetal death in a pregnant woman with prior history of illness consistent with Zika virus infection should raise the suspicion of fetal infection.

While the complete picture of congenital abnormalities that may result from Zika virus fetal infection is still unclear, existing knowledge of other congenital infections (e.g. syphilis, toxoplasmosis, cytomegalovirus, rubella, and herpes) suggests that infected fetuses can present a much wider spectrum of the disease, ranging from being completely asymptomatic to severe involvement of the brain and other organs and even intrauterine fetal death. Therefore, searching for the early appearance of subtle signs of fetal brain abnormalities in association with a positive or inconclusive test for Zika virus is likely to facilitate early diagnosis and appropriate care. Although a normal result of fetal anatomic examination can provide some reassurance for women at potential risk for fetal infection, it cannot predict a normal outcome and subsequent ultrasound reassessment is desirable.

### 3.5.2 Prenatal diagnosis of microcephaly

Fetal microcephaly is a condition in which the fetal head is significantly smaller than expected for gestational age and sex and may be associated with abnormal brain development. Microcephaly is not a disease in itself but a sign of a disease. Health professionals and pregnant women should be aware that prenatal ultrasound diagnosis of this condition is not straightforward and most cases of microcephaly diagnosed at birth or later in life may not be identified during pregnancy.(40) Microcephaly is a rare congenital disorder and the possibility of false positive diagnosis is high, particularly if less conservative thresholds are used. While there is no absolute quantitative cut-off, fetal head circumference at various levels below the average for the reference population is commonly applied to diagnose fetal microcephaly, with smaller head circumferences increasing the probability of the diagnosis.(41, 42)

Microcephaly should be suspected in fetuses with head circumferences two standard deviations below the mean for gestational age, although, in the absence of serious brain abnormalities, normal neuropsychological development is common in most fetuses after birth. For fetuses with head circumferences three standard deviations below the mean for gestational age, the correlation between microcephaly and impaired neurologic development is higher. A fetal

head circumference five standard deviations below the mean for gestational age is an indication of severe reduction in intracranial size, and an ultrasound diagnosis of microcephaly can be made with a reasonable level of confidence (i.e. "rules in" the diagnosis).(43) These quantitative ultrasound examinations can be made by a sonologist with basic experience in fetal biometric examinations, although identification of associated brain abnormalities may require additional training. As these measurements are related to the average fetal dimensions for gestational age, it is critical to ensure that pregnancies are accurately dated and that the appropriate reference fetal growth curve for the population is used to avoid misdiagnosis.

### 3.5.3 Case definition of Zika virus-related fetal brain/other abnormalities

To facilitate classification of fetal brain/other abnormalities in the context of ongoing Zika virus transmission, the WHO interim guidance development group adopted the following case definition for Zika virus-related fetal brain/other abnormalities:

- Fetal brain/other abnormalities with a molecular or epidemiological link to Zika virus in the absence of other conditions that are known to cause brain/other abnormalities in the fetus.

A molecular or epidemiological link with Zika virus is defined as:

- The pregnant woman is a confirmed case of Zika virus disease; **or**
- The pregnant woman had an unprotected sexual contact with a confirmed case, or a history of symptoms or signs consistent with Zika virus infection and residing/travelling in an area with ongoing Zika virus transmission during her pregnancy; **or**
- Presence of Zika virus in amniotic fluid (identified through amniocentesis and RT-PCR assay); **or**
- Presence of Zika virus in fetal brain tissue (identified postmortem through RT-PCR assay).

Other known causes of fetal brain/other abnormalities that should be ruled out include other congenital infections (e.g. syphilis, toxoplasmosis, cytomegalovirus, rubella, and herpes); exposure to toxic drugs, chemicals and radiation; genetic abnormalities e.g. Down syndrome; fetal malnutrition and placental insufficiency.

## 3.6 Care for pregnant women with possible Zika virus related fetal brain/ other abnormalities

*Summary of evidence*

Review of available data did not find any evidence on the evolution and prognosis of fetal malformations presumably associated with maternal Zika virus infection. Indirect evidence from other intrauterine infections (particularly cytomegalovirus (CMV) infection and toxoplasmosis) that cause similar brain malformations suggests that the presence of fetal or neonatal microcephaly and/or central nervous system involvement is almost universally associated with a poor prognosis, including neurodevelopmental delay, intellectual disability, visual disturbances and neurosensory hearing loss.(44-46) In newborns with symptomatic CMV, microcephaly was identified as the most specific predictor of mental retardation in one study.(47) Fetuses and infants with CMV or toxoplasmosis infections but with normal ultrasound findings are expected to have an excellent prognosis.(46, 48)

Where resources exist, pregnant women with ultrasound evidence of suspected fetal microcephaly and/or other brain abnormalities should be referred for specialized care, regardless of the underlying cause. If brain abnormalities are confirmed on ultrasound and a Zika virus test is positive in maternal serum or an amniocentesis specimen, then it is very likely that the abnormalities are related to Zika virus.

As the head circumference gets smaller, the likelihood of other brain abnormalities and consequently a poorer prognosis increases. In such situations, the woman – and her partner if she wishes – should receive individualized counselling and care. Depending on the severity and certainty of the fetal brain abnormalities and associated prognosis, this could range from specialized antenatal care and serial ultrasound follow-up to monitor any progression of the abnormalities, to a discussion of the potential next steps in managing the pregnancy. It is important to ensure that an affected pregnant woman receives accurate and evidence-based information on the prognosis of the identified abnormalities. The woman – and her partner if she so wishes – should be offered non-directive counselling so that she, in consultation with her health care provider, can make a fully informed choice about the next steps in the management of her pregnancy.

Women who carry their pregnancy to term must receive appropriate care and support to manage anxiety, stress and the birth environment.[e] Plans for care and management of the baby soon after birth should be discussed with the parents during the pregnancy, in consultation with a paediatrician or paediatric neurologist where available.

[e] Additional information on psychosocial support for pregnant women and for families with microcephaly and other neurological complications in the context of Zika virus can be found at http://who.int/csr/resources/publications/zika/psychosocial-support/en/

Women who wish to discontinue their pregnancy should receive accurate information about their options to the full extent of the law,[13] including harm reduction where the care desired is not readily available.

All women, whatever their individual choices with respect to their pregnancies, must be treated with respect and dignity.

## 4. Research priorities

The GDG identified important knowledge gaps that need to be addressed through primary research. Given the paucity of direct evidence for the majority of the priority questions, the group acknowledged that further research may have an impact on the recommendations. The following questions were identified as urgent priorities:

- What is the natural history of maternal and fetal Zika virus infection, and is there any difference in disease susceptibility and progression during pregnancy?
- What is the rate of vertical transmission of Zika virus among infected pregnant women?
  - What is the absolute risk of fetal infection/effects (i.e. brain and other abnormalities) by gestational age at infection, manifestation and severity of maternal symptoms or viraemia, and other possible co-factors; and their evolution and intrauterine progression including miscarriage and stillbirth?
- What are the maternal, fetal and neonatal complications associated with Zika virus infection and their prognosis?
- How does Zika virus coinfection with other flaviviruses influence disease progression and subsequent maternal, fetal and neonatal outcomes?
- In women infected with Zika virus, what are the effective interventions to prevent or reduce mother-to-child Zika virus transmission during pregnancy, labour, childbirth, and the postnatal period?
- How effective and safe are the preventive measures against Zika virus infection targeted at pregnant women, both on the individual and population level?
- What are the perceptions of women of reproductive age and their partners and health care providers on pregnancy risk, consequent health care decisions, and behavioural choices in the context of Zika virus and fetal abnormalities?

## 5. Updating the guidance

These recommendations have been produced under WHO emergency procedures and will remain valid until December 2016. However, in accordance with WHO guideline development procedures, this document will be constantly reviewed and promptly updated following the identification of new evidence that warrants a change in clinical policy and practice. The Department of Reproductive Health and Research at WHO Geneva will be responsible for reviewing this guidance at that time, and updating it as appropriate. WHO welcomes queries and suggestions regarding the content of this guidance. Please email suggestions to mpa-info@who.int.

## 6. Acknowledgements

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## 7. References

1. Paixao ES, Barreto F, da Gloria Teixeira M, da Conceicao NCM, Rodrigues LC. History, Epidemiology, and Clinical Manifestations of Zika: A Systematic Review. *Am J Public Health* 2016; 106(4): 606-12.
2. Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, Pessoa A, et al. Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016; 65(3): 59-62.
3. World Health Organization. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations. 1 Feb 2016 2016. Available at: http://www.who.int/media centre/news/statements/2016/1st-emergency-committee-zika/en/ (Accessed 18 February 2016).
4. Gulland A. Zika virus is a global public health emergency, declares WHO. *BMJ* 2016; 352: i657.
5. Ministério da Saúde (Brazil). Microcefalia - Ministério da Saúde divulga boletim epidemiológico 2015. Available at: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20805-ministerio-da-saudedivulga-boletim-epidemiologico (Accessed 18 February 2016).
6. Tetro JA. Zika and microcephaly: causation, correlation, or coincidence? *Microbes Infect* 2016. doi: 10.1016/j.micinf.2015.12.010.
7. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French

Polynesia, December 2013 and February 2014. *Euro Surveill* 2014; 19(13).

8. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol* 2016; 47(1): 6-7.
9. Mlakar J, Korva M, Tul N, Popovic M, Poljsak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. *N Engl J Med* 2016. doi: 10.1056/NEJMoa1600651.
10. Meaney-Delman D, Hills SL, Williams C, Galang RR, Iyengar P, Hennenfent AK, et al. Zika Virus Infection Among U.S. Pregnant Travelers - August 2015-February 2016. *MMWR Morb Mortal Wkly* Rep 2016; 65(8): 211-4.
11. Brasil P, Pereira JP, Jr., Raja Gabaglia C, Damasceno L, Wakimoto M, Ribeiro Nogueira RM, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro - Preliminary Report. *N Engl J Med* 2016. doi: 10.1056/NEJMoa1602412.
12. Martines RB, Bhatnagar J, Keating MK, Silva-Flannery L, Muehlenbachs A, Gary J, et al. Notes from the Field: Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses - Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 2016; 65(6): 159-60.
13. Broutet N, Krauer F, Riesen M, Khalakdina A, Almiron M, Aldighieri S, et al. Zika Virus as a Cause of Neurologic Disorders. *N Engl J Med* 2016; 374(16): 1506-9.
14. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika Virus and Birth Defects - Reviewing the Evidence for Causality. *N Engl J Med* 2016. doi: 10.1056/NEJMsr1604338.
15. Bowman LR, Donegan S, McCall PJ. Is Dengue Vector Control Deficient in Effectiveness or Evidence?: Systematic Review and Meta-analysis. *PLoS Negl Trop Dis* 2016; 10(3): e0004551.
16. Pileggi VN, Bellissimo-Rodrigues F, Souza JP. Mosquito repellents and other protection measures for prevention of Dengue, Chikungunya and Zika virus disease. *Unpublished data* 2016.
17. McGready R, Hamilton KA, Simpson JA, Cho T, Luxemburger C, Edwards R, et al. Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. *Am J Trop Med Hyg* 2001; 65(4): 285-9.
18. Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich BJ, Travassos da Rosa A, Haddow AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. *Emerg Infect Dis* 2011; 17(5): 880-2.
19. Venturi G, Zammarchi L, Fortuna C, Remoli ME, Benedetti E, Fiorentini C, et al. An autochthonous case of Zika due to possible sexual transmission, Florence, Italy, 2014. *Euro Surveill* 2016; 21(8).
20. Hills SL, Russell K, Hennessey M, Williams C, Oster AM, Fischer M, et al. Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission - Continental United States, 2016. *MMWR Morb Mortal Wkly Rep* 2016; 65(8): 215-6.
21. Mansuy JM, Dutertre M, Mengelle C, Fourcade C, Marchou B, Delobel P, et al. Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen? *Lancet Infect Dis* 2016; 16(4): 405.
22. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. *Emerg Infect Dis* 2015; 21(2): 359-61.
23. Atkinson B, Hearn P, Afrough B, Lumley S, Carter D, Aarons EJ, et al. Detection of Zika Virus in Semen. *Emerg Infect Dis* 2016; 22(5): 940.
24. Chibueze EC, Tirado V, Swa T, da Silva Lopes K, Yo T, Balogun O, et al. Zika virus infection in pregnancy: a systematic review of disease course and complications. *Unpublished data* 2016.
25. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009; 360(24): 2536-43.
26. Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, Lambert AJ, Johnson AJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. *Emerg Infect Dis* 2008; 14(8): 1232-9.
27. Brasil P, Calvet GA, Siqueira AM, Wakimoto M, de Sequeira PC, Nobre A, et al. Zika Virus Outbreak in Rio de Janeiro, Brazil: Clinical Characterization, Epidemiological and Virological Aspects. *PLoS Negl Trop Dis* 2016; 10(4): e0004636.
28. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. *Emerg Infect Dis* 2015; 21(1): 84-6.
29. Campos R, Cirne-Santos C, Meira GL, Santos LL, de Meneses MD, Friedrich J, et al. Prolonged detection of Zika virus RNA in urine samples during the ongoing Zika virus epidemic in Brazil. *J Clin Virol* 2016; 77: 69-70.
30. Musso D, Roche C, Nhan TX, Robin E, Teissier A, Cao-Lormeau VM. Detection of Zika virus in saliva. *J Clin Virol* 2015; 68: 53-5.
31. Calvet G, Aguiar RS, Melo AS, Sampaio SA, de Filippis I, Fabri A, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. *Lancet Infect Dis* 2016.doi: doi:10.1016/S1473-3099(16)00095-5.
32. Rungsiprakarn P, Laopaiboon M, Sangkomkamhang US, Lumbiganon P. Pharmacological interventions for generalised itching (not caused by systemic disease or skin lesions) in pregnancy. *Cochrane Database Syst Rev* 2016; 2: CD011351.
33. Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. *Am J Perinatol* 1997; 14(3): 119-24.
34. Gilboa SM, Ailes EC, Rai RP, Anderson JA, Honein MA. Antihistamines and birth defects: a systematic review of the literature. *Expert Opin Drug Saf* 2014; 13(12): 1667-98.
35. Wilson JM, Jungner YG. Principles and practice of screening for diseases. Public Health Paper Number 34. Geneva: World Health Organization; 1968.
36. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. *Lancet* 2016. doi: doi:10.1016/S0140-6736(16)00651-6.
37. Whitworth M, Bricker L, Mullan C. Ultrasound for fetal assessment in early pregnancy. *Cochrane Database Syst Rev* 2015; 7: CD007058.

38. Alfirevic Z, Sundberg K, Brigham S. Amniocentesis and chorionic villus sampling for prenatal diagnosis. *Cochrane Database Syst Rev* 2003; (3): CD003252.

39. Chibueze EC, Parsons AJ, da Silva Lopes K, Nagata C, Nobuyuki H, Swa T, et al. Accuracy of ultrasound scanning relative to reference tests for prenatal diagnosis of microcephaly in the context of Zika virus infection: a systematic review of diagnostic test accuracy. *Unpublished data* 2016.

40. Leibovitz Z, Daniel-Spiegel E, Malinger G, Haratz K, Tamarkin M, Gindes L, et al. Microcephaly at birth - the accuracy of three references for fetal head circumference. How can we improve prediction? *Ultrasound Obstet Gynecol* 2015. doi: 10.1002/uog.15801.

41. Chervenak FA, Jeanty P, Cantraine F, Chitkara U, Venus I, Berkowitz RL, et al. The diagnosis of fetal microcephaly. *Am J Obstet Gynecol* 1984; 149(5): 512-7.

42. Kurtz AB, Wapner RJ, Rubin CS, Cole-Beuglet C, Ross RD, Goldberg BB. Ultrasound criteria for in utero diagnosis of microcephaly. *J Clin Ultrasound* 1980; 8(1): 11-6.

43. Pilu G, Malinger G. Microcephaly. http://www.visuog.com/Page/view.jsp?id=6499122244886988132 (accessed 19 February 2016).

44. Ancora G, Lanari M, Lazzarotto T, Venturi V, Tridapalli E, Sandri F, et al. Cranial ultrasound scanning and prediction of outcome in newborns with congenital cytomegalovirus infection. *J Pediatr* 2007; 150(2): 157-61.

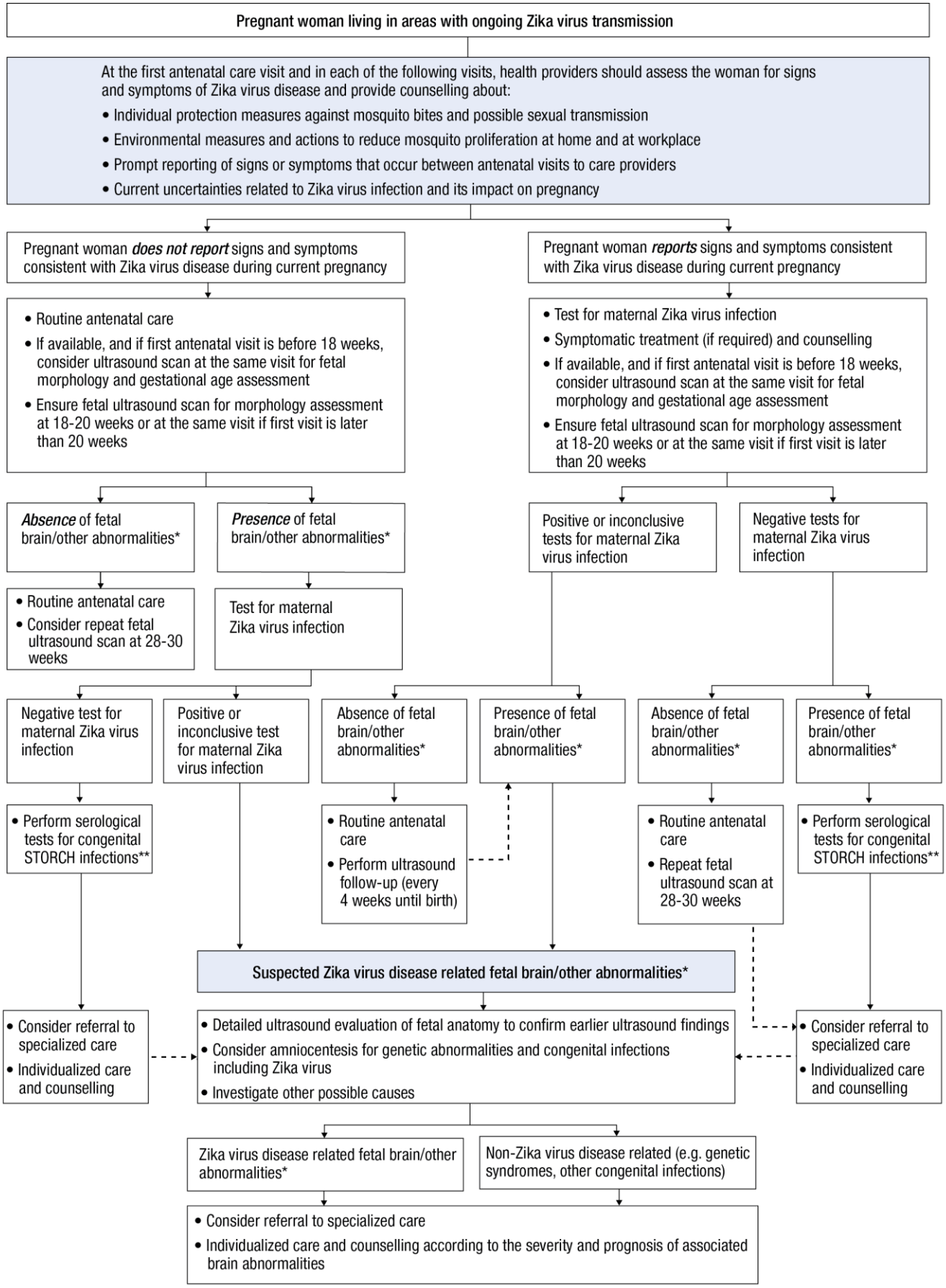
45. Benoist G, Salomon LJ, Jacquemard F, Daffos F, Ville Y. The prognostic value of ultrasound abnormalities and biological parameters in blood of fetuses infected with cytomegalovirus. *BJOG* 2008; 115(7): 823-9.

46. Malinger G, Werner H, Rodriguez Leonel JC, Rebolledo M, Duque M, Mizyrycki S, et al. Prenatal brain imaging in congenital toxoplasmosis. *Prenat Diagn* 2011; 31(9): 881-6.

47. Noyola DE, Demmler GJ, Nelson CT, Griesser C, Williamson WD, Atkins JT, et al. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr* 2001; 138(3): 325-31.

48. Farkas N, Hoffmann C, Ben-Sira L, Lev D, Schweiger A, Kidron D, et al. Does normal fetal brain ultrasound predict normal neurodevelopmental outcome in congenital cytomegalovirus infection? *Prenat Diagn* 2011; 31(4): 360-6.

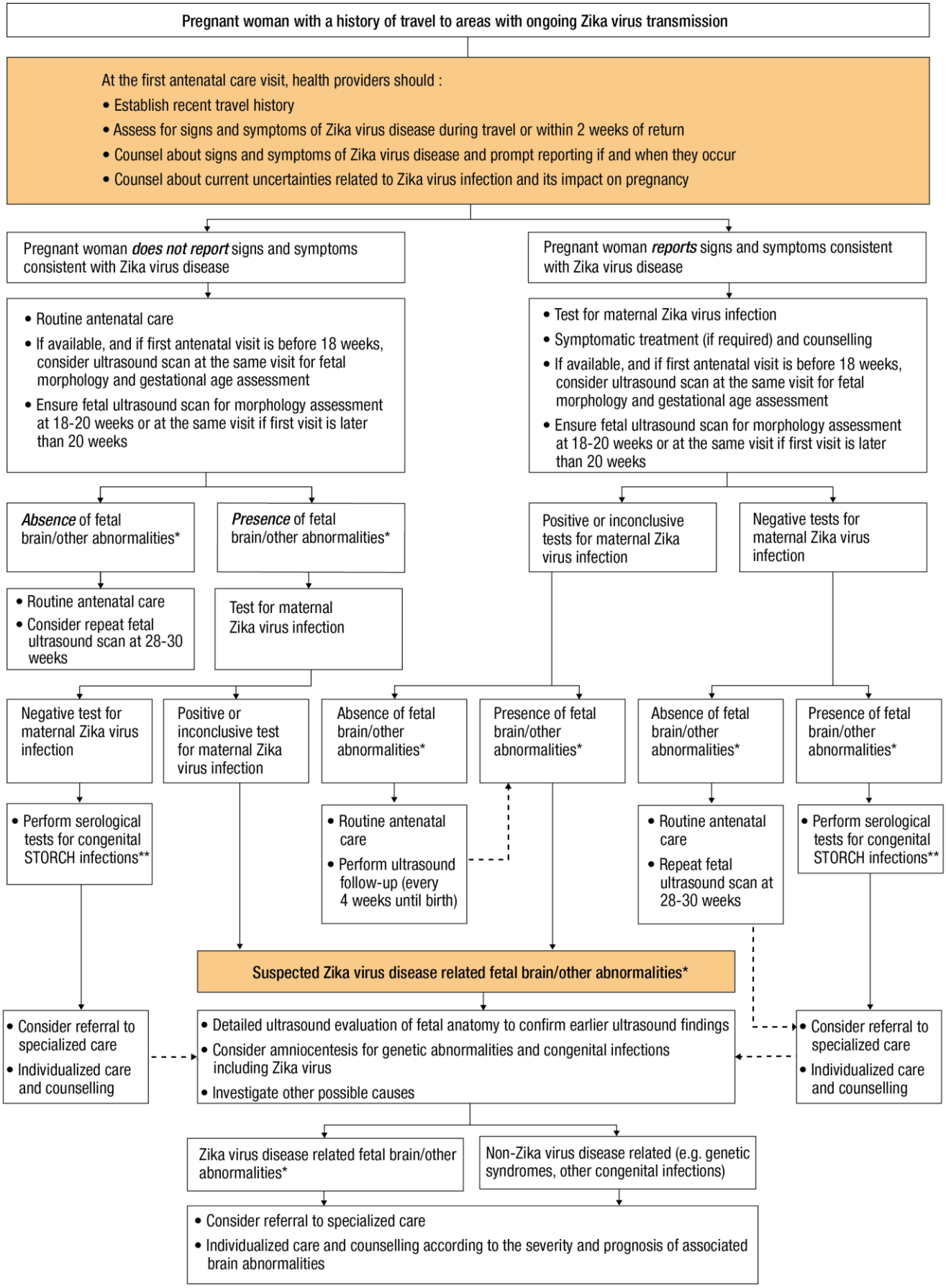
# Annex 1: Decision-chart for the care of pregnant women living in areas with ongoing Zika virus transmission.




* Includes microcephaly, intracranial calcifications, eye calcifications, ventriculomegaly, abnormal sulcation and gyration, brain cerebral atrophy, callosal dysgenesis, failure to visualize different portions of the brain, cerebellar abnormalities, microophthalmia, or arthrogryposis.

** Syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex infections.

# Annex 2: Decision-chart for the care of pregnant women with a history of travel to areas with ongoing Zika virus transmission.




* Includes microcephaly, intracranial calcifications, eye calcifications, ventriculomegaly, abnormal sulcation and gyration, brain cerebral atrophy, callosal dysgenesis, failure to visualize different portions of the brain, cerebellar abnormalities, microophthalmia, or arthrogryposis.

** Syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex infections.

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## Annex 4: Summary of declared interests

All GDG members and external contributors completed a standard WHO declaration of interests (DOI) form before participating in technical consultation or any activities related to development of the guidance. All findings from the received DOI statements were managed in accordance with the WHO conflict of interest guidelines on a case-by-case basis. Participants at the technical consultations also made DOI statements prior to the consultation and no serious conflicts were identified.