

Zika virus

Investigative Guidelines

November 3, 2017

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To characterize the epidemiology, modes of transmission, and clinical aspects of the disease.
2. To monitor disease trends and recognize outbreaks.
3. To identify local transmission within Oregon, should it occur.
4. To identify cases during their infectious period and to prevent transmission to local mosquito vectors and other humans.

1.2 Laboratory and Physician Reporting Requirements

Healthcare providers and laboratories are required to report Zika virus, as an infection that is typically “arthropod vector-borne,” to the local public health department **within one local public health authority working day.**

1.3 Local Health Department Reporting and Follow-Up Responsibilities

1. Report suspect cases to the Oregon Health Authority (OHA) within one local public health authority working day.
2. All cases meeting the suspect case definition should be tested for Zika virus infection. Asymptomatic pregnant women with appropriate exposure history may also be tested in certain situations.
3. All patients for whom testing is requested through the Oregon State Public Health Laboratory (OSPHL) must be entered into Orpheus. Fill out the travel, sexual exposure, symptom, and pregnancy status information in the “Zika Testing Questions.” This information is required for testing approval.
4. Ensure that the provider collects and sends appropriate samples along with appropriate forms to the OSPHL (See § 3.5).
5. Once lab results are received, update case status and complete investigation for those meeting presumptive or confirmed case definitions.
6. Coordinate testing at birth for neonates who are thought to have possible congenital Zika infection.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

Zika virus is a flavivirus transmitted primarily by *Aedes aegypti* and *Aedes albopictus* (the same mosquitoes that transmit dengue, chikungunya and yellow fever viruses). In May 2015, local transmission of Zika virus was confirmed in Brazil. Zika virus infections have been documented in travelers returning to the continental United States and have been locally acquired in isolated areas of the continental U.S. A current list of regions with risk of Zika, including areas with active mosquito transmission and endemic areas, is available here: <http://www.cdc.gov/zika/geo/>.

2.2 Description of Illness

An estimated 80% of persons infected with Zika virus are asymptomatic. Symptomatic infections are generally mild and characterized by fever, maculopapular rash, arthralgia and non-purulent conjunctivitis. Maternal infection during pregnancy can result in intrauterine infection and is associated with fetal loss, microcephaly and other fetal anomalies.¹⁰ Zika virus infection might also lead to Guillain-Barré syndrome (GBS).

2.3 Reservoirs

Humans and non-human primates can serve as reservoirs. Humans are thought to be the primary reservoir during an outbreak.

2.4 Sources and Modes of Transmission

Zika is transmissible via mosquitoes, sexual exposure, from a pregnant woman to her fetus or infant, and via blood-borne exposure.

Aedes aegypti and *Aedes albopictus*, the mosquitoes that transmit Zika, become infected when they feed on a person already infected with the virus, and then spread the virus to other people through bites. These mosquitoes are not found in Oregon.

Zika virus can also be transmitted via sexual exposure, defined as vaginal sex (penis-to-vagina sex), anal sex (penis-to-anus sex), oral sex (mouth-to-penis sex or mouth-to-vagina sex), or sharing of sex toys without a condom. It is unknown how long Zika can persist in semen or vaginal secretions. For updated information, visit CDC's [Zika and Sexual Transmission](#) web page.

A pregnant woman infected with Zika virus can pass the virus to the fetus or to the newborn at the time of birth (i.e., vertical transmission). To date, there are no reports of infants getting Zika virus through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed, even in areas where Zika virus is found.

Zika appears to be transmissible through transfusion of blood products. FDA recommends universal screening of blood products for Zika.²⁵ FDA also recommends that people with symptoms or a positive Zika test wait 120 days to donate blood (whichever is longer).

2.5 Incubation Period

In persons experiencing symptoms, onset of illness typically occurs 3–14 days after exposure.

2.6 Period of Communicability

The periods of communicability for sexual or maternal-fetal transmission are not known. Typically, PCR evidence of Zika virus can be found in the blood of an ill, non-pregnant person for at least a week after the onset of symptoms and for two weeks in urine.¹⁶ Zika virus RNA has been documented in a pregnant woman up to 80 days after clinical onset, but not after delivery.^{11, 29} Moreover, there is some evidence that the virus has been cultured from semen up to 69 days after symptom onset and viral RNA can be shed in semen for at least six months after symptom onset.^{26, 30}

Sexual transmission of Zika virus is possible, and is of particular concern during pregnancy. Although maternal-fetal transmission occurs, it is unclear whether there are particular stages during the pregnancy when transmission is more likely. Lest one be tempted to conclude that congenital Zika infections linked with birth defects are confined to early pregnancy (first trimester), a Brazilian cohort study of pregnant women with Zika infection reported manifestations of congenital Zika infection in situations where maternal infection occurred as late as gestational week 27.¹⁵

2.7 Treatment

There is no specific treatment for Zika virus; treatment is supportive.

2.8 Prevention

There is no vaccine against Zika virus. Currently, the two best ways to prevent Zika virus infection are to avoid exposure to mosquitoes in areas of ongoing transmission and avoid unprotected sexual activity with partners who have recent travel history to a Zika-affected area. The main prevention messages are:

- Pregnant women and women seeking pregnancy should not travel to Zika affected areas.
- People visiting a Zika-affected area should avoid mosquito bites and unprotected sexual contact while there.
- All people returning from regions with active Zika virus transmission should avoid mosquito bites for at least three weeks after returning.
- After possible Zika exposure, people and their sexual partners should avoid unprotected sexual contact for 8 weeks-6 months depending on who traveled (See §6). Those with pregnant partners should avoid

unprotected sexual activity for duration of the pregnancy. For more information about Zika for people considering pregnancy, visit the [CDC webpage](#) 'Women Trying to Become Pregnant'. For information for women who could become pregnant but not seeking pregnancy see [CDC's Preventing Unintended Pregnancy](#) page.

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.0 Possible Exposure to Zika and Window for Testing

Possible exposure to Zika:

- Recent travel to a [Zika-affected area](#); OR
- Unprotected sex with a person who recently traveled to a Zika-affected area or has evidence of Zika infection

NOTE: *Unprotected sex could be a possible exposure to Zika for 8 weeks after a female partner's symptom onset or travel, and for 6 months after a male partner's symptom onset or travel.*

Window for testing:

Specimens should be collected within 12 weeks of symptom onset or possible Zika exposure since testing methods may not be reliable outside of this 12-week window. If a pregnant woman misses the window for testing, serial fetal ultrasounds are an option (every 3–4 weeks). The woman would become eligible for maternal PCR and IgM testing if any Zika-compatible abnormalities are identified by ultrasound. Amniotic fluid may be considered for Zika testing if amniocentesis is planned for other reasons. (See § 4.4).

3.1 Under Investigation Case Definition (meets threshold for testing)

Individuals WHO:

- Are asymptomatic pregnant women (including women who became pregnant within 8 weeks of exposure) with ongoing exposure. Ongoing exposure includes frequent (e.g., at least monthly) travel to a Zika-affected area or unprotected sex with a partner who frequently travels to a Zika-affected area; OR.
- Are born to a mother with Zika infection, but who don't have evidence of infection themselves.

NOTE: *Testing for asymptomatic pregnant women **without** ongoing exposure or prenatal ultrasound findings consistent with congenital Zika virus syndrome is no longer routinely recommended. Testing may be considered based on patient preferences and clinical judgement and should be pursued at private laboratories. Healthcare providers should discuss with their patients the limitations of testing and provide prevention guidance, including avoiding unprotected sex for the duration of the pregnancy.*

3.2 Suspect Case Definition (meets threshold for testing)

Individuals (including pregnant women) WHO:

- Develop clinically compatible illness, which includes one or more of the following symptoms: fever, rash, arthralgia, or conjunctivitis within 2 weeks of possible exposure to Zika; OR
- Are diagnosed with Guillain-Barré syndrome (GBS) within 2 months of possible exposure to Zika; OR
- Are pregnant with or who deliver an infant with abnormalities consistent with congenital Zika syndrome (e.g., microcephaly, intracranial calcifications, or other brain or eye abnormalities) or who experience adverse pregnancy outcomes, including fetal loss following possible exposure to Zika

3.3 Presumptive Case Definitions

Any person who has presumptive serologic evidence of infection as determined by CDC.

3.4 Confirmed Case Definition

Any person who has Zika virus RNA sequence as determined by RT-PCR **OR** confirmatory serologic evidence of Zika virus infection as determined by CDC.

3.5 Services Available at the Oregon State Public Health Laboratory (OSPHL)

OSPHL performs both Zika MAC-ELISA (IgM) and Trioplex rRT-PCR testing for Zika virus. OSPHL can receive and forward specimens for neonates, fetal losses, or other special cases to the CDC. Only patients meeting the CDC's documented testing criteria will be tested through the OSPHL. Patient eligibility for testing must be entered into Orpheus prior to testing at the OSPHL.

Specimens must be accompanied by the following two forms:

- *Oregon Form – Specimen Information for Lab Testing at the CDC* (See: [Submitting Specimens to CDC for Testing.](#))
- *OSPHL Virology/Immunology Test Request Form* (Most clinical labs have this form. If they do not, have them contact the Virology/Immunology section or Client Services Coordinator at the OSPHL, 503-693-4100, to obtain a form.)

3.6 Documenting Zika Testing in Orpheus

All epidemiologic and clinical information listed below must be populated in Orpheus for the specimen to be approved for testing:

Case Basics:

- Demographic information (name, address, DOB, sex, & age)

Zika Testing Questions

- Pregnancy status, last menstrual period (LMP) date and due date if pregnant

- Symptoms and onset date if applicable
- Exact dates and location(s) of travel if applicable and/or exact date of most recent sexual exposure, if applicable

3.7 Interpreting Test Results

Of the two tests conducted for Zika virus infection at the OSPHL, only positive RT-PCR results are considered definitive for confirming Zika infection. IgM may cross-react with *other* flaviviruses (dengue, yellow fever), requiring a confirmatory test. Here's a summary of the various test results and what they mean in terms of case status.

Test	Result	Case status or next steps 1	Case status or next steps 2
RT-PCR	Positive (serum or urine)	<i>Confirmed Case</i>	No additional steps required.
RT-PCR	Negative (both serum and urine)	<p>If symptomatic, test serum by IgM assay.</p> <p>If patient is pregnant and symptomatic, IgM will be done concurrently.</p> <p>If asymptomatic and pregnant with ongoing exposure, run RT-PCR at two additional time points during pregnancy.</p> <p><i>Case status not yet known.</i></p>	<ul style="list-style-type: none"> • If IgM is negative, <i>No Case</i>. • If IgM is positive or equivocal, specimen is forwarded to CDC for additional testing (PRNT) and await their results to determine case status.
IgM ELISA ¹	Presumptive positive, Equivocal or Inconclusive	<p>If patient is <u>pregnant</u>, RT-PCR will be done concurrently.</p> <p>If patient is <u>not pregnant</u>, specimen is forwarded to CDC for PRNT testing.</p> <p><i>Case status not yet known.</i></p>	<ul style="list-style-type: none"> • If PCR is negative, specimen is forwarded to CDC for additional testing (PRNT) and await their results to determine case status.
IgM ELISA	Negative	If tested 2-12 weeks after symptom onset or exposure and RT-PCR is negative, <i>No Case</i> .	No additional steps required.

The OSPHL follows the testing algorithms provided by the CDC. Based on testing algorithms, specimens may be sent to the CDC for confirmatory testing after the OSPHL tests are completed. The purpose of CDC's confirmatory test, called a Plaque

¹ Because IgM antibodies to Zika can persist for a long time in some people, Zika serology is no longer routinely recommended for asymptomatic pregnant women, since it could reflect remote infection that occurred and resolved before pregnancy.

Reduction Neutralization Test (PRNT), is to identify *which* flavivirus was responsible for recent infection. It works relatively well unless someone was infected by two or more flaviviruses or was previously infected by a flavivirus, in which case the infection with Zika cannot be accurately confirmed. PRNT results should be interpreted in the context of the currently circulating flaviviruses in the region where exposure occurred. For more information on testing and interpretation, see: <https://www.cdc.gov/zika/laboratories/lab-guidance.html>

4. SPECIMEN COLLECTION

4.1 Timing of Specimen Collection

See below. Guidance from CDC indicates that the Zika virus might be detectable in the serum of pregnant women longer than in others – which is why they suggest conducting RT-PCR testing on specimens outside of the two-week window for pregnant women only.²²

4.2 Suspect Cases

Collect the indicated specimen(s) based on the number of days between symptom onset and specimen collection according to the chart below for specimens being sent to the OSPHL. If using a different laboratory for Zika testing, follow that laboratory’s instructions.

Urine must be collected the same day as serum.

Time between Symptom Onset and Specimen Collection	What to Collect	What Initial Test to Expect (See §3.7 for reflex test options).
If patient is not pregnant		
< 14 days	3–4 mL of urine AND serum	RT-PCR (Trioplex)
14 days to 12 weeks	1–2 mL of serum	IgM ELISA
If patient is pregnant		
0 to 12 weeks	3–4 mL of urine AND serum	RT-PCR (Trioplex) and IgM ELISA

4.3 Cases under investigation

For cases under investigation in Oregon with ongoing risk of Zika virus exposure test at the following time points according to the chart below.

Pregnancy Time Points	What to Collect	What Test to Expect
Initial case identification	3–4 mL of urine AND serum	RT-PCR
Once during second trimester or timed with prenatal care visit	3–4 mL of urine AND serum	RT-PCR
Once during third trimester or timed with prenatal care visit	3–4 mL of urine AND serum	RT-PCR

4.4 Additional specimen testing (blood, plasma, CSF and amniotic fluid)

The OSPHL can perform PCR testing on additional specimens including blood, plasma, amniotic fluid and cerebrospinal fluid (CSF), and can perform IgM testing on blood, plasma, and CSF. These specimens must be accompanied by a serum sample collected on the same day, so the results can be validated according to the requirements of the testing validation.²² Refer to OSPHL’s test menu for [RT-PCR](#) and [IgM ELISA](#) for detailed information.

4.5 Neonates and Fetal Losses

Coordinate collection of tissue specimens of neonates and fetal losses who are born to women with suspected, presumptive or confirmed Zika infection:

<http://www.cdc.gov/zika/hc-providers/test-specimens-at-time-of-birth.html>

Contact the ACDP Zika Epi so that we can request pre-approval from CDC for specimen and tissue testing. There are additional (non-specimen collection) recommendations to plan for as well (see § 7.2).

5. ROUTINE CASE INVESTIGATION

5.1 If Testing through OSPHL

Testing through OSPHL requires pre-approval from local health authorities and is restricted to those who meet the CDC’s testing guidelines and thresholds (see § 3.1-3.2). An *OSPHL virology form* and completed *CDC Specimen Submission Form* must accompany each specimen. The *CDC Specimen Submission Form* must include symptom onset, exposure dates, symptoms, travel history, travel dates, and specimen collection date as appropriate for the case history.

5.2 If Testing through a Commercial Lab

Commercial labs offer RT-PCR and IgM Zika testing. Providers pursuing Zika testing through a commercial lab should consult the clinical laboratory for send-out options.

For asymptomatic pregnant women who have recent possible Zika exposure but without ongoing exposure, testing may be considered based on patient preference and clinical judgement through commercial laboratories.

5.3 Follow-up for Presumptive and Confirmed Cases

See *Appendix A* for follow-up processes for Zika test results. Lab evidence of infection requires additional case investigation and follow-up with the case and provider (particularly if the case is pregnant).

- Pregnant women
 - Follow-up with provider to review results.
 - Provide patient education. Here are some recommended handouts from CDC:
<https://www.cdc.gov/zika/pregnancy/protect-yourself.html>:
[For Pregnant Women: A Positive Zika Virus Test: What does it mean for me?](#)
[Zika Virus Testing for Any Pregnant Woman Not Living in an Area With Zika](#)
 - See <https://www.cdc.gov/zika/symptoms/diagnosis.html> for translations of these materials
 - Complete additional clinical questions in Orpheus and provide country of birth, race and ethnicity (needed for CDC reporting). Arrange (typically with the case's medical provider) specimen and tissue collection at time of birth.
- Non-pregnant women and all others
 - Follow-up with provider to review results.
 - Provide patient education (avoiding mosquito bites and providing information about pre-conception planning). Here are some recommended handouts from CDC:
<http://www.cdc.gov/zika/symptoms/diagnosis.html>:
[For Nonpregnant Women: A Positive Zika Virus Test: What does it mean for me?](#)
[For Men: A Positive Zika Virus Test: What does it mean for me?](#)
[For Parents: A Positive Zika Virus Test: What does it mean for my child?](#)
 - See <https://www.cdc.gov/zika/symptoms/diagnosis.html> for translations of these materials
 - Complete additional clinical questions in Orpheus and provide country of birth, race and ethnicity.

6. CONTROLLING FURTHER SPREAD ⁴

Prevent secondary/local transmission by urging those who have returned from a Zika-affected area (or a chikungunya or dengue-affected area for that matter) to avoid mosquito bites for three weeks after travel or onset of symptoms. Also remind people to hold off on giving blood for 6 months if they are symptomatic or have lab-confirmed Zika infection.

Pregnant couples are encouraged to use guidance outlined in §7.1 below. Couples who are not pregnant are encouraged to use the guidelines below (regardless of their plans for conception).

Suggested timeframe to wait to seek pregnancy following Zika exposure	
Possible exposure via recent travel or sex without a condom with a person infected with Zika	
Women	Men
Wait at least 8 weeks after symptoms start or last possible exposure	Wait at least 6 months after symptoms start or last possible exposure

7. MANAGING SPECIAL SITUATIONS ⁴

7.1 Pregnancy

Zika infection in pregnancy is associated with problems in fetal development. Congenital infection may be characterized by a pattern of birth defects, classified as congenital Zika syndrome. These features include severe microcephaly, decreased brain tissue, eye defects, joint contractures, and increased muscle tone restricting body movement. Infants with Zika infection who do not have microcephaly at birth may experience slow head growth and develop microcephaly postnatally.

Healthcare providers should screen pregnant women for risk of Zika exposure and symptoms of Zika. Pregnant women should not travel to areas where Zika virus transmission is ongoing. Pregnant women or women seeking pregnancy who do travel to these areas should talk to their healthcare providers and take steps to avoid mosquito bites. Healthcare providers should counsel pregnant women on the interpretation of test results and the limitations of IgM and PCR testing. See CDC guidance here: <https://www.cdc.gov/zika/hc-providers/testresults.html>

Pregnant women or their partners who have lived in or traveled to an area with active Zika virus transmission should abstain from sexual activity or should use

condoms and other barrier methods, e.g., dental dams, during any sexual activity for the duration of the pregnancy. Click on [clinical management](#) to access CDC guidance for care of pregnant women with possible Zika virus exposure.

CDC also recommends that people who are not pregnant but have recent possible Zika exposure wait 8 weeks (if female) or 6 months (if male) before trying to get pregnant. See §6 and additional pre-pregnancy guidance here: <http://www.cdc.gov/zika/pregnancy/women-and-their-partners.html>

7.2 Newborn Care

Healthcare providers should screen pregnant women for risk of Zika exposure, such as travel to a Zika-endemic area or unprotected sex with a partner who has traveled to a Zika-endemic area. If no maternal Zika virus exposure is identified, infants should receive routine pediatric care.

All infants who have possible maternal Zika virus exposure should receive a standard evaluation at birth and at each subsequent well-child visit. A standard evaluation includes a comprehensive physical examination, including growth parameters, age-appropriate vision screening, developmental monitoring, and screening using validated tools.

Testing and clinical evaluation beyond a standard evaluation is not routinely recommended for healthy kids (no abnormal findings on ultrasound or at birth) born to moms who had no laboratory evidence of possible Zika virus infection. This includes moms who had negative test results as well as those who were never tested or tested outside of the appropriate window. However, new findings suggest that infants with no abnormal findings at birth may have underlying brain or other abnormalities, so healthcare providers should remain alert as they care for these children.

Additional testing and follow-up is recommended if maternal or infant Zika test results are positive or if the infant is born with abnormalities consistent with congenital Zika syndrome and has possible maternal Zika virus exposure.

For further information see:

[Updated Recommendations for Infants with Zika](#) (<http://www.cdc.gov/zika/pdfs/pediatric-evaluation-follow-up-tool.pdf>) and <https://www.cdc.gov/zika/hc-providers/infants-children/evaluation-testing.html>

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UPDATE LOG

November 2017: Incorporated new CDC guidance for infants (§7.2). Minor edits for clarity (Takeuchi, Leman)

August 2017: Incorporated new CDC guidance regarding testing of pregnant women. Minor edits for clarity (Takeuchi, Leman)

June 2017: Incorporated new CDC testing guidance for asymptomatic pregnant women. Edits for clarity in case definitions, specimen collection, and congenital Zika syndrome. (Takeuchi, Boyd)

October 2016: Incorporated new CDC guidance on pre-conception planning. Edits for clarity in case definitions. Added Appendix A. (Takeuchi, Boyd, Leman)

August 2016: Incorporated new CDC guidance on testing. Updated to reflect occurrence of isolated mosquito-borne transmission on U.S. Mainland. Edits for clarity in case definitions. (Takeuchi, Boyd, Leman)

July 2016: Updates about urine testing, availability of testing through OSPHL, how to handle Zika testing results from commercial labs, new CDC guidance on testing of asymptomatic pregnant women, Tables added to clarify interpretation of test results (§3.7), timing of specimen collection in different situations (§4.1), and recommended time to wait before attempting pregnancy after potential Zika exposure (§6). Updated to reflect potential sexual transmission by women. Updated references. Minor edits for clarity. (Boyd, Takeuchi, Leman)

May 2016: Updated testing of urine, and GBS case definition. Specified that testing criteria now include suspect cases with epidemiologic risk factors and a single Zika-compatible symptom. (Fisher, Ellingson, Leman)

April 2016: Updated evidence and guidance regarding transmission and testing (Fisher, Ellingson, Leman)

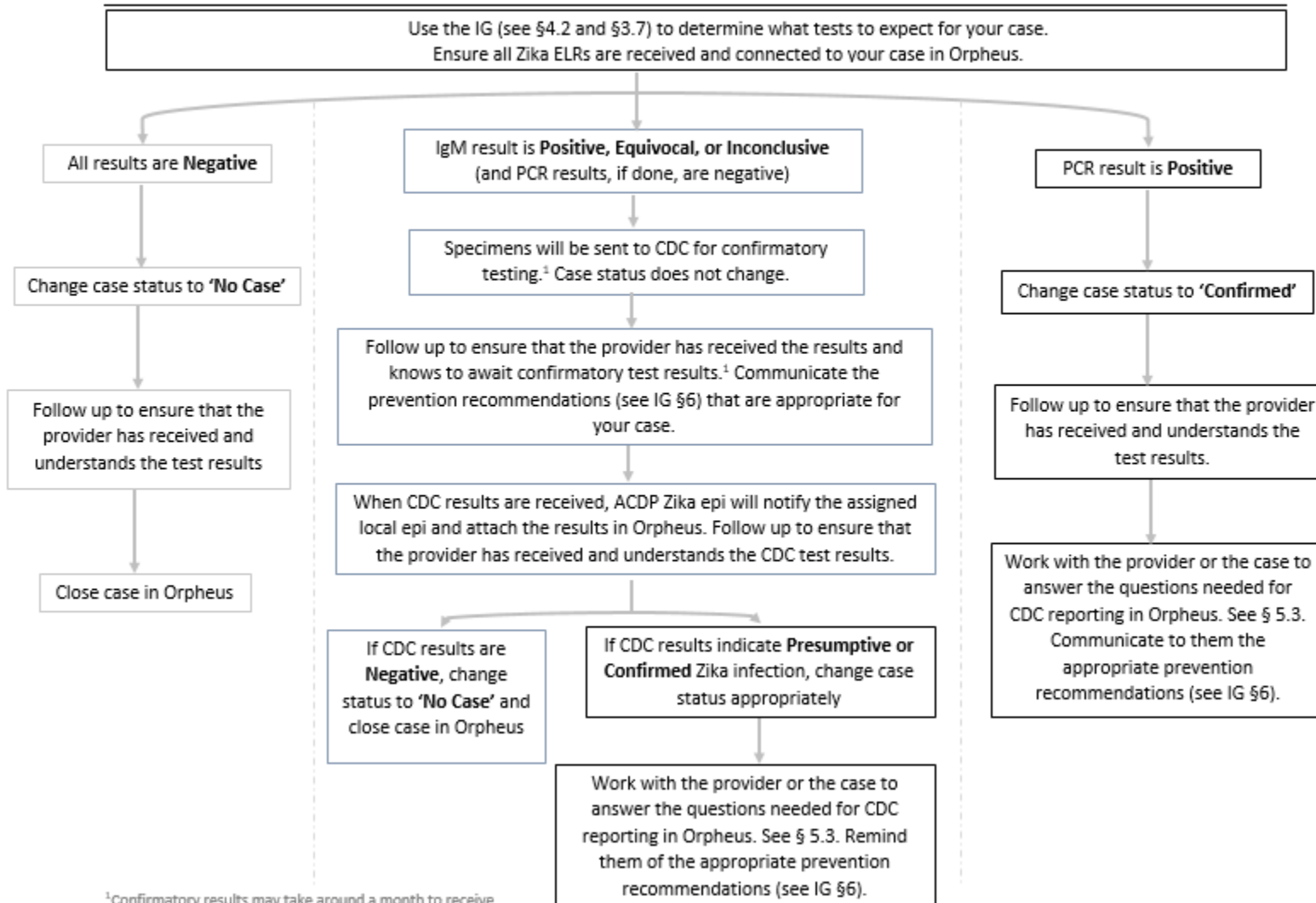
February 26, 2016: Incorporated updated CDC guidance on sexual transmission (Ellingson, Fisher, Leman)

February 18 2016: Incorporated new CDC guidance regarding testing of asymptomatic pregnant women with appropriate travel history, as well as sexual transmission. (Ellingson, Fisher, Leman)

January 2016: Created (Ellingson, Fisher, Leman)

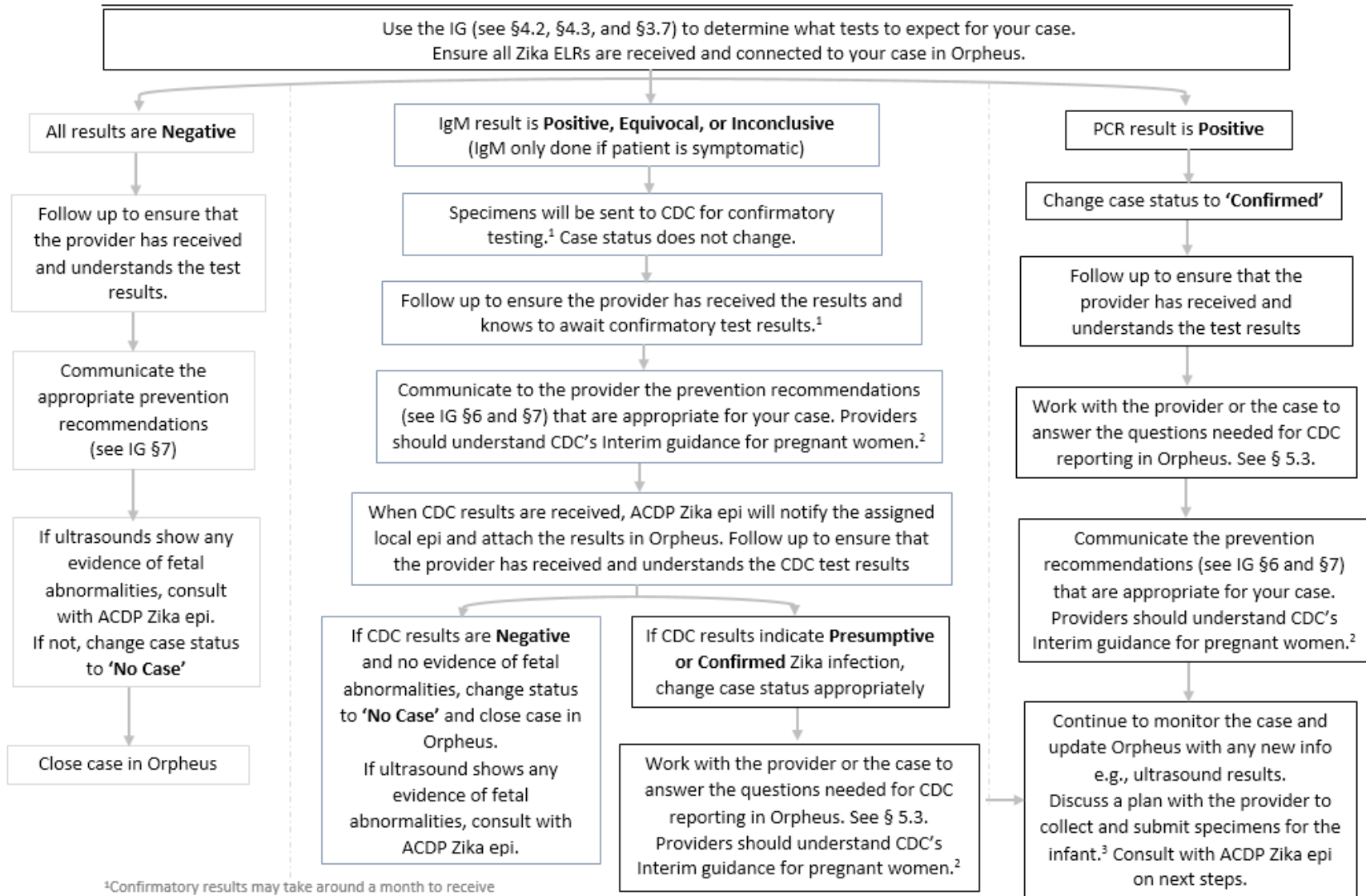
Appendix A

Zika follow-up process for LHDs: **Symptomatic Non-Pregnant Individuals**



¹Confirmatory results may take around a month to receive

Zika follow-up process for LHDs: Pregnant Women



¹Confirmatory results may take around a month to receive

² https://www.cdc.gov/mmwr/volumes/66/wr/mm6629e1.htm?s_cid=mm6629e1_w

³bitly.com/zika-lab