Zika Virus Literature Review (as of July 13, 2016)

Updates since last revision are noted in blue

	Sub-Category	Author	Title	Summary/Key Points	Citation
1.	**Viral Emergence/ Spread**	Duffy MR. et al, 2009	Zika virus outbreak on Yap Island, Federated States of Micronesia, June 2009	• In 2007, physicians on Yap Island (Micronesia) investigated an illness characterized by rash, arthralgia, and conjunctivitis, clinically distinct from dengue. • Illness was identified as Zika virus disease (ZIKV RNA detected in serum). • There were 49 confirmed and 59 probable cases of ZIKV disease identified. • *Aedes hensilli* was the predominant mosquito species identified.	Duffy M, Chen T, Hancock W, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009; 360:2536-43. http://www.nejm.org/doi/pdf/10.1056/NEJMoa0805715
2.	**Viral Emergence/ Spread**	Hayes E, 2009	Zika Virus Outside Africa	• April 2007 first outbreak detected outside of Africa and Asia on Yap Island in the southwestern Pacific. • Studies suggest incubation period in mosquitoes is ~ 10 days. • Virus can be detected in human blood as early as the day of illness onset; viral nucleic acid detected as late as 11 days after onset. • Diagnostic tests should include an acute-phase serum sample and a second sample 2 to 3 weeks after the first. • Viral spread across the Pacific hard to detect due to cross-reactivity of diagnostic flavivirus antibody assays. • Prevention and control should include promotion of insect repellent and interventions to reduce the abundance of potential mosquito vectors.	Edward H. Zika Virus Outside Africa. *Emerging Infectious Diseases.* 2009; 15 (9):1347-1350. doi: 10.3201/eid1509.090442

3.	**Viral Emergence/ Spread**	Musso D. et al, 2014	Rapid Spread of Emerging Zika Virus in the Pacific Area	• Next identified transmission in the Pacific after Yap outbreak of 2007 was in October 2013 in French Polynesia (FP) of which followed a subsequent outbreak of 29,000 cases, closely related to the 2010 and 2007 strains in Cambodia and Yap State (Asian lineage). • Most cases presented with mild symptoms. • November 1 patient developed Guillain-Barre Syndrome (GBS) 1 week after confirmed acute infection of ZIKAV. • Subsequent cases of GBS were identified, with an incidence rate 20-fold higher than expected given the size of the FP population and the established incidence rates of GBS (1-2/100,000 population per year). • Subsequent outbreaks of ZIKAV occurred in New Caledonia, the Cook Islands, and Easter Island.	Musso D, Nilles EJ, Cao-Lormeau VM. Rapid Spread of Emerging Zika Virus in the Pacific Area. *Clin Microbiol Infec.* 2014; 20(10): 0595-6. doi: 10.1111/1469-0691.12707
4.	**Viral Emergence/ Spread**	Musso D. et al, 2014	Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014, April 2014	• During 2013 Zika virus outbreak in French Polynesia, specific nucleic acid testing of blood donors was implemented to prevent ZIKV transmission via blood transfusion. • From November 2013 to February 2014: 42 (3%) of 1,505 blood donors, although asymptomatic at the time of blood donation, were found positive for ZIKAV by PCR. Of the 42 donors tested positive by RT-PCR, 11 declared that they had a Zika fever -like syndrome (rash and/or conjunctivitis and/or arthralgia) from 3 to 10 days after they gave blood. • Findings suggest that ZIKV testing should be used to prevent blood transfusion-transmitted ZIKV, and blood donation safety procedures should be updated to the local epidemiological context.	Musso D, Nhan T, Robin E, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. *Euro Surveill*. 2014; 19(14):1-3 http://www.eurosurveillance.org/images/dynamic/EE/V19N14/art20761.pdf

5.	**Viral Emergence/ Spread**	Tappe D. et al, 2014	First case of laboratory-confirmed Zika virus infection imported into Europe, November 2013, January 2014	• In November 2013, first imported and lab-confirmed ZIKV infection in Europe was diagnosed in a German traveler returning from Thailand. • Symptoms started 12 days after return, and included arthralgia, peri-articular swelling, diffuse maculopapular rash, malaise, fever and chills. • DENV serology was positive for IgM, and negative for IgG. • ZIKV serology was IgM and IgG positive, and RT-PCR detected the viral RNA.	Tappe D, Rissland J, Gabriel M, et al. First case of laboratory-confirmed Zika virus infection imported into Europe, November 2013. *Euro Surveill*. 2014;19(4):1-4. http://www.eurosurveillance.org/images/dynamic/EE/V19N04/art20685.pdf
6.	**Viral Emergence/ Spread**	Campos GS. et al, 2015	Zika Virus Outbreak, Bahia, Brazil	• March 26, 2015- Serum samples obtained from 24 patients in Camacari, Bahia, Brazil. • All patients negative for DENV, Mayaro and WNV. • 7 patients positive for ZIKAV and 3 for CHIKV. • Typical clinical presentation of maculopapular rash, fever, myalgia, and headache. • No simultaneous detection of viruses. • 85.7% of those who tested positive were women; median age 28; no history of travel.	Campos G, Bandeira A, Sardi S. Zika Virus Outbreak, Bahia, Brazil. *Emerg Infect Dis*. 2015; 21(10): 1885–1886. doi: 10.3201/eid2110.150847
7.	**Viral Emergence/ Spread**	Dyer O., 2015	Zika virus spreads across Americas as concerns mount over birth defects, December 2015	• Zika's rapid geographic spread in the Americas is concerning due to its association with neurological conditions such as Guillain-Barre Syndrome and microcephaly. • Brazil's first confirmed Zika infection was in March 2015. Ever since, 2782 microcephaly cases have been identified in Brazil alone. • Timeline: 1947 – ZIKV first isolated from Rhesus monkey in Uganda	Dyer O. Zika virus spreads across Americas as concerns mount over birth defects, December 2015.

				2007: First major Zika outbreak in Yap islands of Micronesia 2013: Bigger outbreak in French Polynesian islands February 2014: First appearance in Western Hemisphere (Chile). March 2015: Major outbreak in Brazil, rapid spread to Americas February 1, 2016: WHO declared Zika virus disease as a Public Health Emergency of International Concern (PHEIC).	*BMJ.* 2015;351:h6983 doi: 10.1136/bmj.h6983
8.	**Viral Emergence/ Spread**	Musso D. et al, 2015	Zika virus: following the path of dengue and Chikungunya? July 2015	• ZIKV is an emerging arthropod-borne virus (arbovirus) that is related to DENV and CHIKV with overlapping clinical features, and similar epidemiology and transmission cycle in urban and peri-urban environments. • Hence, spread of the disease underscores the potential for ZIKV to spread globally, similar to dengue (DENV) and chikungunya (CHIKV) viruses.	Musso D, Cao-Lormeau VM, Gubler D. Zika virus: following the path of dengue and Chikungunya? *Lancet*. 2015;386:243-4. http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(15)61273-9.pdf
9.	**Viral Emergence/ Spread**	Zanluca C. et al, 2015	First report of autochthonous trans-mission of Zika virus in Brazil, June 2015	• First report of Zika virus (ZIKV) in Brazil: Early 2015, in 8 patients with rash, fever, conjunctivitis, and arthralgia, and RT-PCR positive for ZIKV. • ZIKV emergent since 2007.	Zanluca C, Melo VC, Mosimann AL, Dos Santos GI. Mem Inst Oswaldo Cruz. First report of autochthonous trans-mission of Zika virus in Brazil. *Mem Inst Oswaldo Cruz.* 2015; Jun;110(4):569-

					72. doi: 10.1590/0074-02760150192
10.	**Viral Emergence/ Spread**	Brasil P et al, 2016	Zika Virus Outbreak in Rio de Janeiro, Brazil: Clinical Characterization, Epidemiological and Virological Aspects	• First report of a ZIKV outbreak in the state of Rio de Janeiro, based on a large number of suspected (n = 364) and laboratory confirmed cases (n = 119) • 364 suspected cases of Zika virus disease were identified based on clinical criteria between January and July 2015 • 262 (71.9%) were tested and 119 (45.4%) were confirmed by the detection of ZIKV RNA. All of the samples with sequence information available clustered within the Asian genotype • More than half of the patients reported headache, arthralgia, myalgia, non-purulent conjunctivitis, and lower back pain, consistent with the case definition of suspected ZIKV disease issued by the Pan American Health Organization (PAHO). However, fever, when present, was low-intensity and short-termed. • Authors suggest pruritus, the second most common clinical sign presented by the confirmed cases, should be added to the PAHO case definition, while fever could be given less emphasis	Brasil P, Calvet GA, Siqueira AM, Wakimoto M, de Sequeira PC et al. Zika Virus Outbreak in Rio de Janeiro, Brazil: Clinical Characterization, Epidemiological and Virological Aspects. *PLoS Negl Trop Dis.* 2016 Apr 12;10(4):e0004636. doi:10.1371/journal.pntd.0004636
11.	**Viral Emergence/ Spread**	Christofferson RC, 2016	Zika Virus Emergence and Expansion: Lessons learned from Dengue and Chikungunya may not provide all the answers	• Zika virus is transmission is similar to both dengue (DENV) and chikungunya (CHIKV) arboviruses • Studies have shown a high co-occurrence of neutralizing antibody to DENV and CHIV. • The current circulation of ZIKV in Brazil coincides with endemic ENDV and recent CHIKV. • ZIKV is a member of the Japanese encephalitis virus (JEV) serocomplex, thus, there may be cross-reactivity and potential cross-neutralization to other members of the JEV group; evidence suggests cross-reaction with DENV, while some evidence points away from cross-reactivity of the enzyme-linked immunosorbent assay for IgM and IgG in ZIKV acute and convalescent serum samples with DENV.	Chrostofferson RC. Zika Virus Emergence and Expansion: Lessons learned from Dengue and Chikungunya may not provide all the answers. *Am J Trop Med Hyg.* 2016: February [Epub ahead of

				• In the last decade, 11 reported outbreaks of ZIKV have been associated with the Asian genotype (with the exception of Gabon 2007 and Senegal 2011). • Only two of the past 11 outbreaks have had the vectors identified: *Ae. albopictus* and Aedes hensilii*; Aedes aegypti* is attributed to the ongoing transmission in the Americas • The host range of ZIKV outbreaks is more diverse than that of DENV or CHIKV with nine *Aedes* mosquitos species efficiently transmitting the virus as well as *Anopheles* species. Expansion of *Ae. albopictus* gives potential the expansion of transmission in more temperate regions. • In addition to transmission via infectious bites, ZIKV has been detected in urine and saliva, there are reports of sexual and perinatal transmission- these alternate means of transmission suggest that ZIKV emergence may be more complex than DENV and CHIKV transmission systems. • Recent surges in microcephaly incidence in Brazil have coincided with the emergence of ZIKV • There were nearly 2,300 cases of returned traveler-associated CHIKV in 2014 and over 550 in 2015 as of the writing of this review (received for publication in November 2015).	print] http://www.ajtmh.org/content/early/2016/02/18/ajtmh.15-0866.long
12.	**Viral Emergence Spread**	Dirlikov E et al, 2016	Update: Ongoing Zika Virus Transmission - Puerto Rico, November 1, 2015-April 14, 2016.	• During November 1, 2015 to April 14, 2016, a total of 6,157 specimens from suspected Zika virus-infected patients were evaluated by the Puerto Rico Department of Health (PRDH) and CDC Dengue Branch. • 683 (11%) had laboratory evidence of current or recent Zika virus infection by one or more tests: reverse transcription–polymerase chain reaction (RT-PCR) or immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA). • 65 (10%) symptomatic pregnant women tested positive for Zika virus. • 17 (2%) patients required hospitalization, including 5 (1%) patients with suspected Guillain-Barré syndrome. One (<1%) patient died after developing severe thrombocytopenia. • Virus case reporting and diagnostic testing were incorporated into	Dirlikov E, Ryff KR, Torres-Aponte J, et al. Update: Ongoing Zika Virus Transmission — Puerto Rico, November 1, 2015–April 14, 2016. MMWR Morb Mortal Wkly Rep 2016;65:451–455. DOI: http://dx.doi.org/

				surveillance systems, a laboratory-based Passive Arboviral Diseases Surveillance System and a Guillain-Barre syndrome Passive Surveillance System. • The weekly Zika virus disease case counts gradually increased since late November 2015, whereas incidence of dengue and chikungunya cases remained comparatively low. • The public health response includes increased capacity to test for Zika virus, preventing infection in pregnant women, monitoring infected pregnant women and their fetus for adverse outcomes, controlling mosquitos, and assuring the safety of blood products. • In collaboration with PRDH and CDC a home-based vector control program focused on pregnant women is underway. Women are contacted through WIC clinics, and are offered source reduction services (e.g., removal of water containers that can serve as mosquito breeding sites), larvicide application, and indoor and outdoor residual spraying using deltamethrin.	10.15585/mmwr.mm6517e2
13.	**Viral Emergence Spread**	Faria NR et al, 2016	Zika virus in the Americas: Early epidemiological and genetic findings.	• Study used phylogenetic, epidemiological, and mobility data to quantify ZIKV evolution and explore the introduction of the virus to the Americas • Next-generation sequencing was used to generate seven complete ZIKV coding region sequences from samples collected during the outbreak. • Samples include one from a deceased newborn with microcephaly and congenital malformations collected in Ceará and one from a fatal adult case with lupus and rheumatoid disease from Maranhão state. • Maximum likelihood analysis of complete coding regions from our and other ZIKV genome sequences revealed that all viruses sampled in the Americas, including those from Brazil, form a robust monophyletic cluster (bootstrap score =94%) within the Asian genotype • The estimated date of origin in Brazil coincides with an increase in air passengers to Brazil from ZIKV-endemic areas, as well as with reported outbreaks in the Pacific Islands • Municipality-level incidence data indicate that reports of suspected	Faria NR, Azevedo RD, Kraemer MU, Souza R, et al. Zika virus in the Americas: Early epidemiological and genetic findings. *Science* 2016; 352 (6283): 345-349 http://science.sciencemag.org/content/sci/352/6283/345.full.pdf

				microcephaly in Brazil best correlate with ZIKV incidence around week 17 of pregnancy, although this correlation does not demonstrate causation	
14.	**Viral Emergence/ Spread**	Hahn MB et al, 2016	Reported Distribution of *Aedes (Stegomyia) aegypti* and *Aedes (Stegomyia) albopictus* in the United States, 1995-2016 (Diptera: Culicidae)	• Records were compiled using CDC's ArboNET database, VectorMap, published literature, a survey of mosquito control agencies, university researchers, and health departments, for the presence of *Ae. aegypti* and *Ae. albopictus* in the US from 1995-2016 with the goal to represent the current distributions of these mosquitoes. • *Aedes aegypti* or *Ae. albopictus* was considered "present" in a county in a given calendar year if at least one specimen of any life stage of the mosquito was collected, using any collection method, during that year; counties were also classified based on whether a species was collected in 1, 2, or 3 or more years, with no distinction of whether or not collection years were consecutive. • Between January 1, 1995 and December 31, 1999, occurrence of *Ae. aegypti* was reported from 11 counties in Arizona, Texas, and Florida. • In 2004, *Ae. aegypti* was reported from 80 counties and records were added along the southern tier as well as sporadically along the East coast. • By 2009, the number of counties from which the occurrence of *Ae. aegypti* was reported had increased to 109, but the reported geographic distribution of the mosquito had not changed appreciably. • Overall, between January 1995 and March 2016, 183 counties from 26 states and the District of Columbia reported occurrence of Ae. aegypti, and 1,241 counties from 40 states and the District of Columbia reported occurrence of *Ae. albopictus*. • In addition, *Ae. aegypti* was collected in 3 or more years from 94 counties from 14 states and the District of Columbia, and *Ae. albopictus* was collected during 3 or more years from 514 counties in 34 states and the District of Columbia. • The authors concluded that there is a need for systematic surveillance	Hahn MB, Eisen RJ, Eisen L, et al. Reported Distribution of Aedes (Stegomyia) aegypti and Aedes (Stegomyia) albopictus in the United States, 1995-2016 (Diptera: Culicidae). J Med Entomol. 2016 Jun 9. pii: tjw072. DOI: 10.1093/jme/tjw072 [Epub ahead of print]

				of *Ae. aegypti* and *Ae. albopictus* in the US.	
15.	**Viral Emergence/ Spread**	Hennessey M. et al, 2016	Zika Virus Spreads to New Areas — Region of the Americas, May 2015–January 2016, January 2016	• Outbreak began in 2007: Yap State, Federated States of Micronesia, Southeast Asia, and Western Pacific. • May 2015: First local transmission in Americas, including Brazil. • By January 2016: Further spread to more than 19 countries in the Americas (e.g., Puerto Rico). • Transmission types: (1) Mosquito-to-human, (2) intrauterine, (3) intrapartum, (4) sexual, (5) blood transfusion, and (6) laboratory exposure. • ZIKV can cause microcephaly and fetal losses. • Increasing number of imported cases in the US which can result in local transmission in the US.	Hennessey M, Fischer M, Staples JE. Zika Virus Spreads to New Areas — Region of the Americas, May 2015–January 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65:55–58. doi: http://dx.doi.org/10.15585/mmwr.mm6503e1
16.	**Viral Emergence/ Spread**	Kindhauser et al, 2016	Zika: the origin and spread of a mosquito-borne virus	• Timeline of Zika virus-related events, including a map, are summarized from 1947 to Feb 7, 2016. • Transmission of Zika virus infections has been and will most likely continue to be transmitted via the *Aedes* mosquito vectors through international travel. • There have been rare instances of perinatal transmission and sexual transmission via semen. • There has been reported character change of the human Zika virus infection during its geographical expansion- from endemic, mosquito-borne infection causing mild illness from Africa to Asia; from 2007 onwards large outbreaks; from 2013 outbreaks linked to GBS and microcephaly from pacific region to the Americas.	Kindhauser MK, Allen T, Frank V, Santhana RS. Zika: the origin and spread of a mosquito-borne virus. *Bull World Health Organ. E-pub*. 2016. doi: http://dx.doi.org/10.2471/BLT.16.171082

17.	**Viral Emergence/ Spread**	PAHO, 2016	Zika, a new threat. What is it? [Video] Pan American Health Association (PAHO). PAHO TV Video. 2016, January, 2016.	• Zika cases observed in Brazil in 2014 through 2015, and more recently (2015) in Columbia. • The disease is less severe than dengue, but diffuse or localized rash and non-secreting conjunctivitis are the most common and distinguishing clinical features. Conjunctivitis usually lasts 5 to 6 days. Other features include joint pain and swelling, fever (mild), general malaise. • Brazil is developing research protocols to study acute phase of illness and long-term complications. • In Columbia, lab testing is done to rule out measles apart from dengue and Chikungunya. • Preventive measures include destroying potential mosquito breeding sites. • Video of clinical signs, such as maculopapular rash and conjunctivitis shown.	Zika, a new threat. What is it? [Video] Pan American Health Association (PAHO). PAHO TV Video. https://www.youtube.com/watch?v=M8mWDIPKW28&list=PL6hS8Moik7ku3DbBOSoK1p3_E_B_JBRAW&index=1 Published January 13, 2016. Accessed February 15, 2016.
18.	**Viral Emergence/ Spread**	Paixao E. et al, 2016	History, Epidemiology, and Clinical Manifestations of Zika: A Systematic Review	• Systematic review of the literature using MEDLINE, Embase, and Global Health Library, as well as the epidemiological bulletins and alerts from the World Health Organization, the Pan American Health Organization, and the European Centre for Disease Prevention and Control over the period 1954 to 2016 • Of initial 547 records, 52 were systematically reviewed • Cases presented as a mild nonspecific disease; the most common symptoms were rash, fever, arthralgia, conjunctivitis, myalgia, and headache; • 55% of the case reports described Zika in travelers. • As in French Polynesia, there was an increase in the number of neurological manifestations and GBS occurred in Brazil. • In Bahia, the proportion of neurological complications temporally associated with Zika was 2.3 per 1000 (proportion estimated with reported cases); GBS was diagnosed in 1 of every 1000 reported cases. • Previously the annual average was 163 (5.6 per 100 000 live births)	Paixao ES, Barreto F, Teixeira M, et al. History, Epidemiology, and Clinical Manifestations of Zika: A Systematic Review. *Am J Public Health*. 2016; Apr; 106(4):606-12. doi: 10.2105/AJPH.2016.303112

				cases of microcephaly • In 2015, there were 3530 (121.7 per 100 000 live • births) suspected cases of microcephaly reported including 46 deaths, mainly in Pernambuco, a state that concentrated 35% of the total of suspected cases of microcephaly • Among 35 infants with microcephaly, born from women suspected to have Zika infection during pregnancy in northeast Brazil, 74% of the mothers reported rash during the first and second trimester. • Currently, autochthonous Zika transmission has occurred in 27 counties in the Americas including Colombia	
19.	**Viral Emergence Spread**	Petersen L,et al, 2016	Zika Virus	• In 1947 Zika virus was first isolated from the blood of a sentinel rhesus macaque that had been placed in the Zika Forest of Uganda • After 70 years, the virus was introduced into Brazil from the Pacific Islands and spread rapidly throughout the Americas within a year • Only 13 naturally acquired cases were reported from 1953 to 2007, at which time an outbreak occurred in in the State of Yap, Federated States of Micronesia, resulting in 5000 infections among a population of only 6700 • In 2013-14, an outbreak in French Polynesia involved 32,000 people • Map detailing areas for which Zika virus affected humans is noted in article • By September 2015, investigators in Brazil noted an increase in the number of infants born with microcephaly in the same areas in which Zika virus was first reported,38 and by mid-February 2016, more than 4300 cases of microcephaly had been recorded (some inflation probable) • In addition to transmission via mosquito bites, (a map detailing the approximate ranges of A. aegypti and A. albopictus in the United States as of March 2016 is noted in article), new evidence supports transmission via perinatal infection and sexual contact • All strains currently associated with the outbreak in the Americas are	Petersen L, Jamieson D, Powers A, Honein M. Zika Virus. N Engl J Med. 2016 Mar DOI: 10.1056/NEJMra1602113

				of the Asian genotype and are most closely related to strains from Yap, Cambodia, Thailand, and French Polynesia • Clinical aspects consist of acute febrile illness, neurological complications, and adverse fetal outcomes, most notably microcephaly • The mainstays of the routine diagnosis of Zika virus infection are the detection of viral nucleic acid by RT-PCR and the detection of IgM antibodies by IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA).	
20.	**Viral Emergence Spread**	Schnirring L, 2016	Cuba, Dominica report local Zika; study estimates US risk	• Cuba announced first local case in 21 year old woman • Dominica announced its first confirmed case in an individual with no travel history • According to researchers, the *Aedes* aegypti mosquito populations will become more abundant across much of the South and East in the US, and that Zika virus outbreaks are a risk for US cities from NYC to LA during the peak summer months (findings are published in *Public Library of Science Currents Outbreaks*). • In regards to travel patterns, it is predicted that cities in southern Florida and impoverished parts of southern Texas could be hard hits (see National Center for Atmospheric Research map). • Of note, the confirmed number of cases of microcephaly in Brazil at the time of this publication was 854.	Schnirring, L. Cuba, Dominica report local Zika; study estimates US risk. Center for Infectious Disease Research and Policy. http://www.cidrap.umn.edu/news-perspective/2016/03/cuba-dominica-report-local-zika-study-estimates-us-risk Published March 16, 2016. Accessed April 5, 2016.

21.	**Viral Emergence Spread**	Waddell LA et al, 2016		• A literature review on Zika virus studies was conducted through March 1, 2016, resulting in a total of 233 studies analyzed and the majority of these were published since 2011. • The majority of articles covered the topics of epidemiology of ZIKV; pathogenesis; and molecular characterization and in vitro evaluation. Most studies were found to have used observational study designs. • Knowledge gaps identified were ZIKV epidemiology, the importance of potential non-human primates and other hosts in the transmission cycle, the burden of disease in humans, and complications related to human infection with ZIKV.	Waddell LA, Greig JD (2016) Scoping Review of the Zika Virus Literature. PLoS ONE 11(5): e0156376. doi:10.1371/journal.pone.0156376
22.	**Co-Morbidities/ Complications**	Oehler E. et al, 2014	Zika Virus Infection Complicated by Guillain-Barre Syndrome- Case Report, French Polynesia, December 2013	• November 2013, during ZIKA and Dengue co-epidemic, a 40 year French Polynesian woman was treated for GBS. 7 days prior to GBS presentation, patient had developed myalgia, febricula, cutaneous rash, and conjunctivitis. • Laboratory tests ruled out common etiologies for GBS. RT-PCR was negative for ZIKAV 8 days after the beginning of the influenza-like symptoms; blood samples on day 8 and 28 after the influenza-like symptoms were positive for ZIKA-specific IgM and ZIKA, and DENV-specific IgG.	Oehler E, Watrin L, Larre P, et al. Zika virus infection complicated by Guillain-Barré syndrome – case report, French Polynesia, December 2013. *Euro Surveill*. 2014;19(9):20720. doi: http://dx.doi.org/10.2807/1560-7917.ES2014.19.9.20720
23.	**Co-Morbidities/ Complications**	Cao-Lormeau V. et al, 2016	Guillain-Barre Syndrome outbreak associated with Zika virus infection in French	• Case-control study including 42 patients diagnosed with Guillain-Barre syndrome (GBS) in French Polynesia between outbreak period of October 2013, and April 2014. • Control groups consisted of age, sex, and residence-matched patients with a non-febrile illness (control group 1; n=98) and age-matched patients with acute zika virus and no neurological symptoms (control	Cao-Lormeau V, Blake A, Mons S, et al. Guillain-Barre Syndrome outbreak associated with

			Polynesia: a case-control study	group 2; n=70) • 98% of 42 patients diagnosed with GBS had anti-zika IgM or IgG, and 100% had neutralizing antibodies vs 56% of 98 in control group 1. • 39 (93%) patients with GBS had zika virus IgM and 37 (88%) had transient illness in a median of 6 days before onset of neurological symptoms; rash, arthralgia and fever were the most commonly reported symptoms • The risk of GBS based on a 66% attack rate of zika virus infection in the general population, was estimated to be 0-24 per 1000 Zika virus infections • 12 patients required respiratory assistance • No reported deaths • Anti-glycolipid antibody activity was found in 13 (31%) of patients • Typical AMAN-associated anti-ganglioside antibodies were rarely present • All cases of GBS received treatment by immunoglobulins, and one cases had plasmapheresis • Past dengue virus history had no significant difference in patients with GBS vs the two control groups.	Zika virus infection in French Polynesia: a case-control study. *Lancet*. 2016: Feb 29 [Epub ahead of print] doi: 10.1016/S0140-6736(16)00562-6
24.	**Co-Morbidities/ Complications**	Ortega L et al, 2016	Fatal Virus Infection in Girl with Sickle Cell Disease, Colombia	• 15 year old female medical history significant for sickle cell disease (diagnosed at age 10, no previous history of acute chest syndrome or hospitalizations) presented with fever, arthralgia, retro-ocular pain, abdominal pain, myalgia, and jaundice for 4 days • Initially diagnosed with DENV infection • Clinical symptoms worsened with patient developing respiratory distress, severe abdominal pain hepatomegaly, and splenomegaly, cardiac abnormalities; patient was admitted to intensive care unit and intubated • RT-PCR was positive for ZIKV infection • Despite blood transfusions and intensive treatment, patient expired 37 hours after initial presentation • Autopsy significant for hepatic panacinar necrosis,	Arzuza-Ortega L, Polo A, Pérez-Tatis G, et al. Fatal Zika virus infection in girl with sickle cell disease, Colombia [letter]. *Emerg Infect Dis.* 2016. http://dx.doi.org/10.3201/eid2205.151934

				erythrophagocytosis of Kupffer cells, and functional asplenia with drepanocytes and splenic sequestration	
25.	**Co-Morbidities/ Complications**	Ventura CV et al, 2016	Zika virus in Brazil and macular atrophy in a child with microcephaly, January 2016	• Authors report ophthalmic findings in three infants with microcephaly born after the ZIKV outbreak in Brazil. • All three infants had cerebral calcifications, and unilateral ocular findings affecting the macular region. • Ocular findings included gross macular pigment mottling and foveal reflex loss, and macular neuro-retinal atrophy. • One infant's mother reported rash and arthralgia in the first trimester. None of the mothers had ocular lesions.	Ventura CV, Maia M, Bravo-Filho V, Góis A, Belfort R. Zika virus in Brazil and macular atrophy in a child with microcephaly. *Lancet*. 2016; 387:228 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00006-4/fulltext.
26.	**Perinatal Transmission**	Tsai TF, 2006	Congenital arboviral infections: something new, something old, March 2006	• Review of vertical arboviral transmissions causing congenital neurological anomalies: Japanese Encephalitis Virus (JEV), West Nile Virus (WNV), St. Louis Encephalitis Virus (SLEV), Western Equine Encephalitis virus (WEE), Venezuelan Equine Encephalitis Virus (VEEV), and Eastern Equine Encephalitis (EEE) virus.	Tsai TF. Congenital arboviral infections: something new, something old. *Pediatrics.* 2006;117(3):936-9. http://www.ncbi.nlm.nih.gov/pubmed/?term=Congenital+Arboviral+Infections%3A+Somet

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27.	**Perinatal Transmission**	Besnard M. et al, 2014	Evidence of Perinatal Transmission of Zika Virus, French Polynesia, December 2013 and February 2014	• 2 reported cases of perinatal transmission; possible routes of infection: transplacental, delivery, breastfeeding or close contact (i.e., saliva). • Mother #1 possibly viremic before and during delivery; delivered vaginally, newborn remained healthy up to 5 days post-delivery. • Mother #2 possibly viremic or incubating during delivery; pregnancy complicated by gestational diabetes and intrauterine growth restriction; delivery by caesarean; newborn born with severe hypotrophy, 8/9/9 Apgar and jaundice; developed rash on day 3 post-caesarean. • Sera from both mothers were positive within 2 days post-delivery; infants sera positive within 4 days post-delivery. • Both newborns had similar RNA loads in serum; however, newborn #1 remained asymptomatic. • Newborn #2 displayed low platelet count and elevated total bilirubin on day 3. • Breast milk samples from both mothers positive for ZIKAV; however, cell culture was negative for replicative ZIKAV. • Conclusion: transplacental vs delivery transmission cannot be distinguished as there is no firm data on the delay necessary for ZIKAV to become detectable by RT-PCR; detection in breast milk samples shows possible transmission; saliva samples from positive for RT-PCR shows possible contamination by close contact.	Besnard M, Lastère S, Teissier A, Cao-Lormeau VM, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. *Euro Surveill.* 2014;19(13):20751. doi: http://dx.doi.org/10.2807/1560-7917.ES2014.19.13.20751
28.	**Perinatal Transmission**	Silasi M. et al, 2015	Viral Infections During Pregnancy	• Complications from viral infections (i.e., preterm labor) in pregnancy thought to be a result of subsequent polymicrobial infections- viral infection of the placenta may affect the normal interaction with local bacteria, causing a pro-inflammatory “cytokine storm” which leads to preterm delivery.	Silasi M, Cardenas I, Kwon JY, Racicot K. Viral Infections During Pregnancy. *Am J Reprod*

				• Demonstrated by murine model in which pregnant mice were inoculated with murine herpes virus. All mice delivered preterm; significant inflammatory responses were also noted in the placenta and decidua in addition to reported adverse fetal outcomes.	*Immunol*. 2015;73(3):199-213. doi: 10.1111/aji.12355
29.	**Perinatal Transmission**	Bayer A et al, 2016	Type III Interferons Produced by Human Placental Trophoblasts Confer Protection against Zika Virus Infection	• Authors investigated the mode of ZIKV infection of primary human trophoblasts (PHTS) (barrier cells of the placenta) • This studied showed that primary human trophoblast (PHT) cells, isolated from full-term placentas, are refractory to infection by two strains of ZIKV, one derived from an African lineage, and one derived from an Asian lineage that exhibits > 99% amino acid sequence similarity to strains currently circulating in Brazil. • The authors also found that conditioned medium (CM) isolated from PHT cells protected non-trophoblast cells from ZIKV infection through the constitutive release of the type III IFN IFNl1. • Authors conclude that primary human placental trophoblasts are refractory to ZIKV infection due to their release of antiviral type III interferons, which also serves to protect non-placental cells; suggesting that ZIKV possibly uses alternative strategies to cross the placenta rather than directly infecting the placenta.	Bayer A, Lennemann NJ, Ouyang YU, Bramley JC, et al. Type III Interferons Produced by Human Placental Trophoblasts Confer Protection against Zika Virus Infection. Cell Host Microbe. 2016 May 11;19(5):705-12. doi: 10.1016/j.chom.2016.03.008
30.	**Perinatal Transmission**	Brasil P. et al, 2016	Zika Virus Infection in Pregnant Women in Rio de Janeiro-Preliminary Report	• A total of 88 women whom had developed a rash within the previous 5 days were tested via blood and urine specimens by RT-PCR and followed prospectively • Acute viral infection ranged from 5 to 38 weeks gestation • Of the 88 women, 72 (82%) tested positive in one or both samples; 60 women had positive serum specimens; 46 had positive urine specimens; 34 had positive samples in both specimens; 12 had had positive results in urine specimens only, and 26 had positive results in blood specimens only • Clinical features were typical of Zika virus infection	Brasil P, Pereira J, Gabaglia C, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro-Preliminary Report. *N Engl J Med.* 2016 Mar 4 [Epub ahead of

				• Among positive women, more than half reported similar illnesses other family members, and 21% reported that their partner had been ill • More than half the women presented with acute infection in the second trimester of pregnancy • 2 positive women miscarried during the first trimester • Fetal ultrasound was performed in 42 positive women; Fetal abnormalities were detected in 12 of the positive women • 5 of the 12 fetuses had intrauterine growth restriction, with or without accompanying microcephaly; 4 fetuses had cerebral calcifications and other CNS alteration in 2 fetuses; abnormal arterial flow in the cerebral or umbilical arteries was seen in 4 fetuses; oligohydramnios and anhydramnios were seen in 2 fetuses; two fetal deaths occurred in two cases after 30 weeks gestation • At the time of this report, 8 of the women who received an u/s have delivered (6 live and 2 stillbirths)	print] DOI: 10.1056/NEJMoa1602412
31.	**Perinatal Transmission**	Cauchemez S. et al, 2016	Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study	• Retrospective study which used serological and surveillance data to estimate the probability of infection with Zika virus for each week of the epidemic using medical records to identify all cases of microcephaly from September, 2013, to July, 2015. • A total of 8 cases of microcephaly were identified. • (88%) occurred in the 4-month period March 1 to July 10, 2014. • Of the six periods of risk during pregnancy, four explained the timing of cases of microcephaly significantly better than the no association model. The two that did not perform significantly better than the no association model assumed the period of risk was restricted to trimester three or trimesters two and three. • The timing of these cases was best explained by a period of risk in the first trimester of pregnancy where the baseline prevalence of microcephaly was two cases (95% CI 0–8) per 10 000 neonates, and the risk of microcephaly associated with Zika virus infection was 95 cases (34–191) per 10 000 women infected in the first trimester.	Cauchemez S, Besnard M, Bompard P, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. 2016 Mar 15. pii: S0140-6736(16)00651-6. doi:10.1016/S0140-6736(16)00651-6

				• Increased risk of microcephaly could not be ruled out in other trimesters, but models that excluded the first trimester were not supported by the data.	
32.	**Perinatal Transmission**	CDC Media Statement, 2016	CDC Concludes Zika Causes Microcephaly and Other Birth Defects	• Scientists at the Centers for Disease Control and Prevention (CDC) have concluded, after careful review of existing evidence, that Zika virus is a cause of microcephaly and other severe fetal brain defects via a report in the NEJM *Zika Virus and Birth Defects — Reviewing the Evidence for Causality* *http://www.nejm.org/doi/pdf/10.1056/NEJMsr1604338* • The report notes that no single piece of evidence provides conclusive proof that Zika virus infection is a cause of microcephaly and other fetal brain defects. Rather, increasing evidence from a number of recently published studies and a careful evaluation using established scientific criteria supports the authors' conclusions.	CDC Concludes Zika Causes Microcephaly and Other Birth Defects. CDC Media Statement April 13, 2016 http://www.cdc.gov/media/releases/2016/s0413-zika-microcephaly.html
33.	**Perinatal Transmission**	Chibueze EC et al, 2016	Zika virus infection in pregnancy: a systematic review of disease course and complications	• Systematic review conducted using MEDLINE, EMBASE, CINAHL, WHO Global Health Library, Cochrane Central Trials Register, and Cochrane Database from inception until March 2016 • Objective was to characterize ZIKV infection, including its natural • history, risk of adverse outcomes in pregnant women, and describe the range of associated clinical manifestations and associated abnormalities. • Of 142 eligible full-text articles, 18 met inclusion criteria (13 case series and five cohorts) • The authors included all studies reporting on ZIKV infection and complications in pregnant women residing in or with a history of travel to areas of ongoing ZIKV transmission or recent ZIKV outbreaks. • There was no noted greater risk of infection in pregnant vs non-pregnant; common symptoms consisted of fever, rash, and arthralgia; GBS only reported severe maternal morbidity; fetal/newborn complications included fetal and newborn neurological and ocular abnormalities; fetal growth restriction, stillbirth and perinatal death, with microcephaly the man neurological complication reported in 8	Chibueze EC, Tirado V, da Silva Lopes K, Balogun OO, Takemoto Y, Swa T, et al. Zika virus infection in pregnancy: a systematic review of disease course and complications [Submitted]. Bull World Health Organ. E-pub: 9 June 2016. doi: http://dx.doi.org/10.2471/BLT.16.1

				studies. Some studies reported not maternal symptoms during infection and some studies reported normal birth outcomes.	78426
34.	**Perinatal Transmission**	Driggers R.W. et al., 2016	Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities	• 33 yo Finnish woman infected during the 11th week of gestation while visiting Mexico, Guatemala, and Belize. • Serologic analysis that was performed 4 weeks after the onset of illness while she was on a trip to her native Finland was positive for IgG antibodies and negative for IgM antibodies against dengue virus. • Subsequent serologic analysis was positive for both IgG and IgM antibodies against ZIKV. • Serologic analysis for the presence of chikungunya virus was negative. • Noted decrease in the fetal head circumference from the 47th percentile at 16 weeks to the 24th percentile at 20 weeks, along with an abnormal intracranial ultrasound and MRI at 20 weeks gestation. • Pregnancy was terminated at 21 weeks of gestation. • Maternal serum that was obtained on the day before termination was positive for ZIKV RNA with a low viral count (2.1×103 copies • per milliliter). • No ZIKV RNA was detected in the serum, peripheral-blood mononuclear cells, saliva, or urine in samples obtained 11 days and 13 days after termination. • In detecting ZIKV RNA in the serum of a pregnant woman at 4 weeks and 10 weeks after the clinical onset of ZIKV infection but not after delivery, the authors suggest that the persistent ZIKV viremia in the patient described was a result of viral replication in the fetus or placenta, which had high viral loads. • The authors thus suggest the use of quantitative RT-PCR methods for diagnostic approach for ongoing placental or fetal infections in pregnant women (of note, ZIKV RNA levels were higher in the maternal serum than in the amniotic fluid)	Driggers RW, Ho CY, Korhonen EM, Kuivanen S, et al. Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities. N Engl J Med. 2016 Jun 2;374(22):2142-51. doi: 10.1056/NEJMoa1601824

35.	**Perinatal Transmission**	Franca GV et al, 2016	Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation	• In Brazil, a total of 1501 infants born between November 19, 2015 and February 27, 2016 received full investigations. • Suspected cases included live newborn babies with microcephaly defined as 33 cm or less for term boys and girls, which was reduced to 32 cm on Dec 12. • There were 5 categories (1) definite, or newborns with evidence of Zika infection during pregnancy via PCR or serology, independent of other findings; the other 4 categories included newborns without laboratory evidence: (2)highly probable, or newborns with specific imaging reports and negative for syphilis, toxoplasmosis, and cytomegalovirus; (3)moderately probable, or newborns with specific imaging reports but positive for one or more of the three infections; (4) somewhat probable, or newborn babies with imaging reports lacking a detailed description of the findings, for which a state-level physician concluded that a congenital infection was likely involved, for whom laboratory results for the three infections were negative or unavailable; (5) discarded cases, or newborns not included in any of the cases. • 899 cases were discarded; of the remaining 602 cases, 76 were definite, 54 highly probable, 181 moderately probable, and 291 somewhat probable of congenital Zika virus syndrome. • Compared with these four groups, the 899 discarded cases had larger head circumferences (mean Z scores -1·54 vs -3·13, difference 1·58 [95% CI 1·45-1·72]); lower first-week mortality (14 per 1000 vs 51 per 1000; rate ratio 0·28 [95% CI 0·14-0·56]); and were less likely to have a history of rash during pregnancy (20·7% vs 61·4%, ratio 0·34 [95% CI 0·27-0·42]). • Brain abnormalities despite normal sized heads, were associated with rashes in the 3rd trimester. One in five definite or probable cases presented head circumferences in the normal range (above -2 SD below the median of the Inter-Growth standard) and for one third of definite and probable cases there was no history of a rash during pregnancy.	França GV, Schuler-Faccini L, Oliveira WK, et al. Congenital Zika virus syndrome in Brazil: a case series of the first 1501 livebirths with complete investigation. Lancet. 2016 Jun 29. pii: S0140-6736(16)30902-3. doi: 10.1016/S0140-6736(16)30902-3. [Epub ahead of print]

				• The peak of the epidemic occurred in late November, 2015. • The authors conclude that Zika virus congenital syndrome is a new teratogenic disease which must be detected with revised screening criteria given that many cases (definite and probable) present normal head circumference values and there is no report of rash with the mother.	
36.	**Perinatal Transmission**	Johansson MA et al., 2016	Zika and the Risk of Microcephaly	• Population-level data from French Polynesia and Bahia reveal a clear association between first-trimester ZIKV infection and microcephaly risk. • To estimate the magnitude of the risk of microcephaly in Brazil, data from Bahia was analyzed • In this analysis, it was assumed that the infection rate in Bahia could range from 10 to 80% on the basis of estimates from Yap and French Polynesia (66 to 73%) and reports from non-outbreak ZIKV sero-surveys (6 to 40%) • The authors apportioned the risk across 2015 according to the temporal distribution of reported cases, assumed that all pregnant women were equally susceptible, to infection, and assessed the association of infection risk with microcephaly cases reported in the Brazilian Live Births Information System between July 2015 and February 2016 (as of March 21, 2016, accounting for a reporting delay and assuming that all reported births occurred at full term). • A strong association between the risk of microcephaly and infection risk in the first trimester and a negligible association in the second and third trimesters, in keeping with the associations found in population-level estimates for French Polynesia, was found. • Authors reported that the estimated baseline risk of microcephaly was low, approximately 2 per 10,000 births, but the estimated risk due to infection in the first trimester ranged from 0.88% (95% credible interval, 0.80 to 0.97), when they assumed an 80% overall ZIKV infection rate and 100% over-reporting of microcephaly cases, to 13.2% (95% credible interval,12.0 to 14.4), when they assumed a 10% ZIKV infection rate and no over-reporting.	Johansson MA, Mier-Y-Teran-Romero L, Reefhuis J, Gilboa SM, Hills SL. Zika and the Risk of Microcephaly. N Engl J Med. 2016 May 25 [Epub ahead of print] DOI: 10.1056/NEJMp1605367

37.	**Perinatal Transmission**	Martines B. et al 2016	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	• More than 4,700 suspected cases of microcephaly were reported from mid-2015 through January 2016, although additional investigations might eventually result in a revised lower number • December 2015, formalin-fixed, paraffin-embedded (FFPE) tissues samples from two newborns with microcephaly (born at 36 and 38 weeks gestation) who died within 20 hours of birth, and two miscarriages (fetal losses at 11 and 13 weeks) were submitted to CDC, from Rio Grande do Norte in Brazil • All four mothers had fever, rash, during the first trimester of pregnancy; all were negative for clinical signs of active infection delivery or miscarriage • Samples from all four cases were positive for RT-PCR • In newborns only brain tissue was positive for RT-PCR • Placental tissue from one miscarriage showed heterogeneous chorionic villi with calcification; chorionic villi sampling was normal for the other miscarriage • Viral antigen was noted in mononuclear cells (presumed to be glial cells and neurons within the brain) of one newborn, and within the chorionic villi from one of the miscarriages • It is concluded that brain and early gestational placental tissue might be the preferred tissues for postmortem viral diagnosis. • Non-frozen, formalin-fixed specimens or FFPE blocks are the preferred sample type for histopathologic evaluation and immunohistochemistry • RT-PCR can be performed on either fresh frozen or formalin-fixed specimens.	Martines RB, Bhatnagar J, Keating MK, 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;65:1–2. doi: http://dx.doi.org/10.15585/mmwr.mm6506e1er
38.	**Perinatal Transmission**	Meaney-Delman D, et al. 2016	Zika Virus Infection Among U.S. Pregnant Travelers — August 2015–February 2016	• On January 19, 2016, CDC released interim guidelines recommending that pregnant women who had traveled to areas with ongoing local transmission of Zika virus and who had symptoms consistent with Zika virus disease be tested for Zika virus infection; these were updated on February 5 to offer Zika virus testing to all pregnant women with Zika virus exposure, regardless of the presence of symptoms • Between August 1, 2015 – February 10, 2016, the CDC received 257	Meaney-Delman D, Hills SL, Williams C, et al. Zika Virus Infection Among U.S. Pregnant Travelers —

				requests for testing of ZIKV for pregnant women. • As of February 17, 2016, only nine of the pregnant women were determined to be positive for Zika virus infection. All reported a clinical illness, including eight women with ≥2 signs and/or symptoms, and one with a generalized rash. • Six pregnant women with Zika virus disease who reported symptoms during the first trimester, had the following outcomes: early pregnancy losses (2), elective pregnancy terminations(2), and delivery of a live born infant with microcephaly (1); one pregnancy is continuing. • Among two women with Zika virus infection who had symptoms during the second trimester of pregnancy, one apparently healthy infant has been born and one pregnancy is continuing. One pregnant woman reported symptoms of Zika virus infection in the third trimester of pregnancy, and she delivered a healthy infant.	August 2015–February 2016. MMWR Morb Mortal Wkly Rep 2016;65:211–214. DOI: http://dx.doi.org/10.15585/mmwr.mm6508e1
39.	**Perinatal Transmission**	Melo AS et al, 2016	Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? January, 2016	• Zika virus disease including microcephaly outbreak was noted in Brazil in 2015. • By 28 November 2015, 646 cases had been reported in Pernambuco state, Brazil alone. • Two microcephaly cases were examined: (1) in case 1, fetal ultrasound at 30.1 gestational weeks showed head circumference (HC) 2.6 SD below expected value, brain atrophy, and course white matter calcifications. (2) In case 2, HC at 29.2 weeks' gestation was 3.1 SD below expected value, with brain atrophy, ventriculomegaly, cataracts, and intraocular calcifications. • Six microcephaly cases studied were born to mothers who had Zika symptoms during pregnancy, and all cases had HC below the 10th percentile. • Apart from ZIKV disease, other intrauterine infections that can retard fetal brain development include cytomegalovirus (CMV), toxoplasmosis, herpes virus, syphilis, rubella, and West Nile encephalitis virus (flavivirus). Among these, Zika virus related fetal brain atrophy and microcephaly closely resembles CMV and West Nile encephalitis virus disease.	Melo AS, Malinger G, Ximenes O, Szejnfeld PO. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol.* 2016; 47:6–7 http://onlinelibrary.wiley.com/doi/10.1002/uog.15831/epdf

40.	**Perinatal Transmission**	Mlakar J. et al, 2016	Zika Virus Associated with Microcephaly	• 25-year-old previously healthy female working in Natal, Rio Grande do Norte presented in Slovenia in mid-October 2015 due to assumed fetal anomalies. • At 13 weeks of gestation patient had previously reported fever, severe musculoskeletal and retroocular pain, itching and generalized maculopapular rash. • Ultrasonography that was performed at 14 and 20 weeks of gestation showed normal fetal growth and anatomy. • At 29 weeks, first abnormal ultrasound was noted; subjective decreased fetal movement. • At 32 weeks, ultrasound confirmed intrauterine growth retardation with numerous calcifications otherwise normal, microcephaly, moderate ventriculomegaly, and a transcerebellar diameter below the second percentile. • Brain structures were blurred with noted numerous calcifications • Pregnancy terminated at 32-weeks of gestation; autopsy significant from microcephaly • Positive results for ZIKV were obtained on RT-PCR assay only in the fetal brain sample; all autopsy samples were tested on PCR assay and were found to be negative for other flaviviruses • Concluded that findings suggest vertical transmission	Mlakar J, Korva M, Tul N, et al. Zika Virus Associated with Microcephaly. [Brief Report]. *NEJM*. 2016; doi: 10.1056/NEJMoa1600651
41.	**Perinatal Transmission**	Oduyebo T. et al, 2016	Update: Interim Guidelines for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016, February	• Update: Serologic testing for ZIKV offered to asymptomatic pregnant women with a history of travel to an area with ongoing Zika virus transmission. Testing offered 2-12 weeks after return from travel. • Pregnant woman with travel history → Tested for ZIKV→ Test positive or inconclusive →Consider (1) fetal ultrasounds, and (2) amniocentesis for ZIKV testing. • Pregnant woman with travel history → Tested for ZIKV→ Test negative for ZIKV →Fetal ultrasound to detect microcephaly or intracranial calcifications →(1) If either findings are present, then consider retesting mother for ZIKV, and offer amniocentesis for ZIKV testing; and (2) if none of the findings are present, then continue with	Oduyebo T, Petersen E, Rasmussen S, et al. Update: Interim Guidelines for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika

			2016	routine prenatal care. • For pregnant women with clinical illness consistent with Zika virus disease, testing is recommended during the first week of illness. • Asymptomatic pregnant women residing in Zika-affected areas can be offered IgM testing upon initiation of prenatal care; with repeat testing considered in the mid-second trimester due to the ongoing risk for Zika virus exposure throughout pregnancy. • Pregnant women whose male partners have or are at risk for Zika virus infection should consider using condoms or abstaining from sexual intercourse.	Virus Exposure — United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2016;65:1-6. http://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6505e2er.pdf
42.	**Perinatal Transmission**	Oliveira, Wanders et al, 2016	Increase in Reported Prevalence of Microcephaly in Infants Born to Women Living in Areas with Confirmed Zika Virus Transmission During the First Trimester of Pregnancy- Brazil, 2015	• By January 2016, transmission had been confirmed in 22 of Brazil's 26 states and the federal district, and in all five regions of the country; this was a major increase from 2015, occurring largely in the Northeast region of the country where the Zika outbreak first began. • By October 29th, 2015, an increase in the number of microcephaly cases was reported by the Brazil Ministry of Health (MoH) as a potential Public Health Emergency of International Concern. • The case definition for microcephaly changed from a head circumference of ≤33cm to ≤32cm in any full-term newborn; which is currently used nationwide. • Conducted by the MoH and Secretaries of Health from the affected areas, an analysis of 574 cases of microcephaly, was detected through a newly established ad hoc microcephaly surveillance system which identified temporal and geospatial evidence linking the occurrence of febrile rash illness consistent with Zika virus disease during the first trimester of pregnancy with the increased birth prevalence of microcephaly. • The prevalence of microcephaly in 15 states with laboratory/RT-PCR-confirmed Zika virus transmission (2.8 cases per 10,000 live births) significantly exceeded that in four states without confirmed Zika virus transmission (0.6 per 10,000). • Of the 574 cases, 58.5% (336) were females	Oliveira W, Cortez-Escalante J, Oliveira Wanessa, et al. Increase in Reported Prevalence of Microcephaly in Infants Born to Women Living in Areas with Confirmed Zika Virus Transmission During the First Trimester of Pregnancy- Brazil, 2015. *MMWR Morb Mortal Wkly Rep*. Mar 8, 2016; 65. http://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6509e2er.pdf

				• The average head circumference was 29.0 cm	
43.	**Perinatal Transmission**	Pacheco O et al, 2016	Zika Virus Disease in Colombia — Preliminary Report	• Patients with clinical symptoms of ZVD from August 9, 2015, to April 2, 2016, were included in the analysis; a subset of pregnant women were included in the analysis of pregnancy outcomes. • A total of 65,726 cases of ZVD were reported in Colombia; 2485 (4%) were confirmed via RT-PCR. • 11,944 pregnant women with ZVD were reported in Colombia, with 1484 (12%) confirmed via RT-PCR assay. • In a subgroup of 1850 pregnant women, more than 90% of women infected during the third trimester had no infants with apparent abnormalities. • From January 1, 2016, to April 28, 2016, a total of 50 infants with possible microcephaly were reported to the national surveillance system for birth defects; of these cases of microcephaly, four had laboratory evidence of congenital ZVD; all were born to asymptomatic mothers who were not included in the ZVD surveillance system. • Authors conclude that that maternal infection with the Zika virus during the third trimester of pregnancy is not linked to structural abnormalities in the fetus. However, the monitoring of the effect of ZVD on pregnant women in Colombia is ongoing.	Pacheco O, Beltrán M, Nelson CA, et al. Zika Virus Disease in Colombia - Preliminary Report. N Engl J Med. 2016 Jun 15. DOI: 10.1056/NEJMoa1604037 [Epub ahead of print]
44.	**Perinatal Transmission**	Panchaud A et al, 2016	Emerging Role of Zika Virus in Adverse Fetal and Neonatal Outcomes	• WHO declared a Public Health Emergency of International Concern in February 2016. • In April 2016, CDC announced the existence of a causal relationship between prenatal ZIKV and microcephaly along with other neurological abnormalities. • Despite the growing number of cases with maternal signs of infection and/or presence of ZIKV in tissues of affected newborns or fetuses, the authors assess that it is currently difficult to determine the magnitude of increase of microcephaly prevalence in Brazil, as well as the role of	Panchaud A, Stojanov M, Ammerdorffer A, Vouga M, Baud D. Emerging Role of Zika Virus in Adverse Fetal and Neonatal Outcomes. Clin Microbiol Rev.

				other factors in the development of congenital neurological conditions. • Authors describe microcephaly, infectious agents known to cause birth defects, the investigation of the causal link between Zika virus and birth defects, clinical management, counseling women of reproductive age and pregnant patients, and challenges with (lack of) data and the current outbreak. • The authors suggest that new mutations in the Zika virus could impact viral replication in humans, leading to increased virulence and consequently heightened chances of viral transmission to additional naive mosquito vectors • More studies are needed to assess ZIKV and its affect in congenital neurological conditions.	2016 Jul;29(3):659-94. DOI: 10.1128/CMR.00014-16
45.	**Perinatal Transmission**	Peterson E. et al, 2016	Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016, January 2016	• A pregnant woman with a history of travel to ZIKV-affected country is tested for ZIKV infection if has symptoms within 2 weeks of travel. • If test is positive or inconclusive, then fetal ultrasound is performed to detect microcephaly and/or intracranial calcifications; and amniocentesis to test amniotic fluid for ZIKV is offered. • If maternal ZIKV test is negative, fetal ultrasound is performed. And if microcephaly or calcifications are present, then amniotic fluid can be tested for ZIKV. • If pregnant woman with history of travel has no symptoms, then fetal U/S is done to look for microcephaly/calcifications. If either finding is present, mother is tested for ZIKV, and amniocentesis for ZIKV testing is offered. If initial U/S does not have findings, serial ultrasounds (every 3-4weeks) are performed to assess for microcephaly/calcifications. • Maternal-fetal-medicine or infectious disease specialist is consulted for any suspected ZIKV transmission. • Preventive measures: (1) avoid travel to ZIKV affected countries during pregnancy, and (2) if travel is unavoidable, then engage in mosquito bite prevention steps, such as use of permethrin-treated clothing and gear.	Petersen EE, Staples JE, Meaney-Delman, D, et al. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65:30–33. doi: http://dx.doi.org/10.15585/mmwr.mm6502e1

				• Treatment is entirely supportive: rest, fluids, antipyretics, and analgesics. Rule out Dengue (DENV) before treating with NSAIDS. Avoid NSAIDS in pregnancy.	
46.	**Perinatal Transmission**	Peterson E. et al, 2016	Update: Interim Guidance for Health Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure — United States,	• Women with possible exposure who do not reside in an area with active transmission- Women and men with possible exposure to Zika virus but without clinical illness consistent with Zika virus disease should wait at least 8 weeks after exposure to attempt conception. • Men with possible exposure who do not reside in an area with active transmission- Men should wait at least 6 months after symptom onset if they have been diagnosed with Zika virus disease • Women and men with possible exposure to Zika virus but without clinical illness consistent with Zika virus disease should wait at least 8 weeks after exposure to attempt conception. • Women and men who reside in areas with active transmission- Women with Zika virus disease should wait at least 8 weeks from symptom onset before attempting conception; men with Zika virus disease should wait at least 6 months from symptom onset before attempting conception. • Women and men who do not have clinical illness consistent with Zika virus disease and who desire pregnancy should talk with their health care providers • In regards to testing, pregnant women with possible exposure who do not reside in an area with active transmission should be tested according CDC's updated interim guidance Figure 1; pregnant women who do reside in an area with active transmission should be evaluated and tested in accordance with CDC updated interim guidance Figure 2.	Petersen EE, Polen KN, Meaney-Delman D, et al. Update: Interim Guidance for Health Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:315–322. DOI: http://dx.doi.org/10.15585/mmwr.mm6512e2
47.	**Perinatal Transmission**	Rasmussen SA et al, 2016	Zika Virus and Birth Defects — Reviewing the Evidence for Causality.	• To determine whether Zika virus infection during pregnancy causes these adverse outcomes, the authors evaluated data using criteria that have been proposed for the assessment of potential teratogens- Shepard's criteria and Bradford Hill criteria • On the basis of this review using both criteria frameworks, it was concluded that a causal relationship exists between prenatal Zika virus	Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika Virus and Birth Defects —

				infection and microcephaly and other serious brain anomalies. • Evidence that was used to support this causal relationship included Zika virus infection at times during prenatal development that were consistent with the defects observed; a specific, rare phenotype involving microcephaly and associated brain anomalies in fetuses or infants with presumed or confirmed congenital Zika virus infection; and data that strongly support biologic plausibility, including the identification of Zika virus in the brain tissue of affected fetuses and infants.	Reviewing the Evidence for Causality. NEJM. 2016: April http://www.ncbi.nlm.nih.gov/pubmed/?term=Zika+Virus+and+Birth+Defects+%E2%80%94+Reviewing+the+Evidence
48.	**Perinatal Transmission**	Reefhuis J et al, 2016	Projecting Month of Birth for At-Risk Infants after Zika Virus Disease Outbreaks	• To help address questions relating to the numbers of infants with microcephaly reported in Brazil and the absence of reported microcephaly cases in other countries where transmission is high, assessment of the timing of transmission and its relation to gestational week of pregnancy for the cohort of women who were pregnant during the outbreak was performed. • The report illustrates the expected periods of exposure and weeks of delivery for the cohorts of pregnant women potentially infected with Zika virus during outbreaks in Bahia State, Brazil. • Using published data for Bahia State and assuming that all pregnancies lasted 40 weeks (full term), figures were created demonstrating cohorts of pregnant women by week of delivery and then extrapolated to the beginning of pregnancy. • The increased number of reported cases of microcephaly in Bahia State began with October births; reported cases rose sharply during November 2015–January 2016. For the city of Salvador, these November 2015–January 2016 births corresponded to the highest likelihood of infection occurring in the first trimester or early in the second trimester of pregnancy, assuming that the date of report approximates the date of birth. • In Country A, women whose pregnancies began in July 2015 would be expected to deliver in late March and early April 2016, and risk for	Reefhuis J, Gilboa SM, Johansson MA, Valencia D, et al. Projecting Month of Birth for At-Risk Infants after Zika Virus Disease Outbreaks. Emerg Infect Dis. 2016 May;22(5):828-32. doi: 10.3201/eid2205.160290.

				infection would have been highest during the second trimester. • The highest likelihood of first trimester and early second trimester infection would be among women who became pregnant during September 2015–January 2016, which corresponds to births from mid-May through early October 2016. • To enable readers to project months when births with • exposure in different trimesters can be expected, the authors developed a modifiable spreadsheet tool (online Technical Appendix, **http://wwwnc.cdc.gov/EID/article/22/5/16-0290-** • **Techapp1.xlsx**). Users may enter start and end dates of hypothetical outbreaks.	
49.	**Perinatal Transmission**	Schuler-Faccini L. et al, 2016	Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015, January 2016	• By September 2015, there were increasing microcephaly cases reported in Zika-affected countries. • Microcephaly was defined by Brazil Ministry of Health as neonatal head circumference ≥2 SD below the mean for gestational age and sex of the infant at birth. • A task force and registry were established to investigate Zika virus–related cases of microcephaly and to describe the clinical characteristics of cases. Among the first 35 cases of microcephaly, 74% of mothers reported a rash illness during pregnancy, 71% of infants had severe microcephaly (>3 SD below the mean), about half had at least one neurologic abnormality, and among 27 who had neuroimaging studies, all were abnormal.	Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:59–62. doi: http://dx.doi.org/10.15585/mmwr.mm6503e2
50.	**Perinatal Transmission**	Tang H, et al. 2016	Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth	• ZIKV was previously detected in the amniotic fluid of two pregnant women whose fetuses had been diagnosed with microcephaly (Clavet et al, 2016); ZIKV has also been found in microcephalic fetal brain tissue (Mlaker t al, 2016). • The direct target cells of ZIKV in fetal neural tissue is not known • This study used human induced pluripotent stem cells as an in vitro	Tang H, Hammack C, Ogden S, et al. Zika Virus Infects Human Cortical Neural Progenitors and

				model to investigate whether ZIKV directly infects human neural and the nature of its impact • This report shows that a strain of the ZIKV, MR766, serially passaged in monkey and mosquito cells infects human neural progenitor cells (hNPCs) derived from induced pluripotent stem cells • Infections of the hNPCs (which can be further differentiated into cortical neurons) were titered with ZIKV at a low multiplicity of infection (MOI <0.1)and removed after a 2 hr. incubation period. • Infection rates were quantified 56 hrs. later with RT-PCR • The hNPCs were readily infected by ZIKV in vitro, with the infection reaching 65%-90% of the cells within 3 days of inoculation. Analysis showed similar results for hNPCs derived from hiPSC lines of two different subjects • Infected hNPCs further release infectious ZIKV particles • Infection due to ZIKV increases cell death and dysregulates cell-cycle progression, which attenuates hNPC growth	Attenuates Their Growth. [Brief Report] *Cell Stem Cell.* 2016; 18: 1-4. doi: 10.1016/j.stem.2016.02.016
51.	**Perinatal Transmission**	Teixeira, MG., et al, 2016	The Epidemic of Zika Virus-Related Microcephaly in Brazil: Detection, Control, Etiology, and Future Scenarios	• In Brazil, by the end of 2015, 4180 cases of suspected microcephaly had been reported; • Women delivering in October 2015 made up the first trimester of pregnancy at the peak of the outbreak of Zika infection. • In the state of Pernambuco, Brazil, there 26 cases in 3 weeks of newborns with microcephaly in October of 2015. • In epidemiologic wee 44 (November 2015), cases of microcephaly were diagnosed in other states of the northeast region. • Epidemiologic week 49 reported the highest number of cases in a week (900 cases). • By February 2016 Zika epidemic was considered a public health emergency by the WHO. • The evidence for the epidemic of microcephaly resulting from congenital transmission of Zika virus is reflected in the geographical distribution of Zika outbreaks. • Futher evidence points to the presence of Zika virus RNA in amniotic	Teixeira MG, Costa MN, Oliveira WK, Nunes ML. Rodrigues LC. The Epidemic of Zika Virus-Related Microcephaly in Brazil: Detection, Control, Etiology, and Future Scenarios. *AJPH*. 2016; 106(4):607-605. doi: 10.2105/AJPH.2016.303113

				fluid of 2 pregnant women whose fetuses had microcephaly, tissue samples of a deceased case, increases in cases of Guillain-Barre syndrome, found after outbreaks, and cases of microcephaly in women who were pregnant during the Zika outbreak in French Polynesia.	
52.	**Perinatal Transmission**	Villamil-Gomez. WE et al. 2016	Diagnosis, management and follow-up of pregnant women with Zika virus infection: A preliminary report of the ZIKERNCOL Q5 cohort study on Sincelejo, Colombia	• During January 2016, a retrospective preliminary analysis of a cohort of 28 pregnant women with RT-PCR confirmed ZIKV infection admitted to maternity units in Sincelejo, Sucre (north, Caribbean coast region), Colombia were recruited and followed-up. • 21 (75%) reported ZIKV symptoms during pregnancy, 7 (25%) had no reported symptoms. • Serologies were negative for chikungunya and dengue • Infection occurred during first trimester for 1 (4%), second trimester for 12 (43%), and the third for 15 (54%) • Clinical symptoms were typical of arboviral infection (rash, fever, arthralgias, and conjunctivitis) • Ultrasounds in two cases suggested brain calcifications (amniocentesis will be performed on them) as well in one women there was a twin pregnancy. • The group will be further assessed regarding pregnancy outcomes.	Villamil-Gomez WE, Mendoza-Guete A, Villalobos E., et al. Diagnosis, management and follow-up of pregnant women with Zika virus infection: A preliminary report of the ZIKERNCOL Q5 cohort study on Sincelejo, Colombia. [Correspondence] *Travel Med Infect Dis*. 2016; March [Epub ahead of print] doi: 10.1016/j.tmaid.2016.02.004
53.	**West Nile Virus Perinatal Transmission**	Nguyen Q et al., 2002	Intrauterine West Nile Virus Infection - New York, 2002	• First identified case of vertical WNV transmission reported during the 2002 WNV epidemic in the US. Mother was diagnosed with WNV meningoencephalitis during pregnancy with positive serology, and the newborn infant had chorioretinitis and severe cerebral abnormalities including white matter loss, with serum and CSF positive for WNV antibodies.	Nguyen Q, Morrow C, Novick L, et al. Intrauterine West Nile Virus Infection --- New

					York, 2002. *MMWR Morb Mortal Wkly Rep.* 2002;51(50):1135-1136 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5150a3.htm
54.	**West Nile Virus Perinatal Transmission**	Paisley JE et al, 2005	West Nile Virus Infection Among Pregnant Women in a Northern Colorado Community, 2003 to 2004, March 2006	• WNV-specific antibodies in cord blood from infant deliveries were measured to determine the frequencies of WNV infections during pregnancy and of intrauterine WNV infections. • Umbilical cord blood was collected from 549 infants and screened for WNV IgM and IgG antibodies. • Four percent of cord blood samples were IgG positive for WNV. No cord blood samples were IgM positive for WNV. • There were no significant differences between infants of seropositive and seronegative mothers with respect to any of the growth parameters or outcomes measured. • Findings suggested that intrauterine WNV infections seemed to be infrequent. And, WNV infection during pregnancy did not seem to affect adversely infant health at birth.	Paisley JE, Hinckley AF, O'Leary DR, et al. West Nile Virus Infection Among Pregnant Women in a Northern Colorado Community. *Pediatrics*. 2006;117(3):814-20. http://www.ncbi.nlm.nih.gov/pubmed/?term=West+Nile+Virus+Infection+Among+Pregnant+Women+in+colorado
55.	**West Nile Virus Perinatal Transmission**	O'Leary D et al, 2006	Birth Outcomes Following West Nile Virus Infection of Pregnant Women	• 77 women infected with WNV during pregnancy were identified via the CDC and clinically followed. • Of 66 live infants with information regarding physical examination, 7 (10.6%) had major birth defects: aortic co-arctation (following 3rd trimester WNV infection), cleft palate (following 3rd trimester WNV	O'Leary DR, Kuhn S, Kniss KL, et al. Birth Outcomes Following West Nile Virus

			in the United States: 2003-2004	infection), Down syndrome (following 2nd trimester WNV infection), lissencephaly (following 3rd trimester WNV infection), microcephaly (2) (following 2nd trimester WNV infection), and polydactyly (following first trimester WNV infection). • 4 infants had minor birth defects: skin tag (1), umbilical hernia (4); one infant had type 1 glycogen storage disease • Of 55 live infants from whom cord serum was collected, only 1 had anti-WNV IgM at month of age. Serum collected in subsequent months was negative. • Of 46 cord blood specimens and 50 cord tissue specimens tested, all were negative via RT-PCR for WNV • Only 1/50 placentae tested positive for RT-PCR; the mother was negative (mother had onset of WNV 4 days prior to delivery)	Infection of Pregnant Women in the United States: 2003-2004. *Pediatrics*. 2006;117(3):e537-45. http://www.ncbi.nlm.nih.gov/pubmed/16510632
56.	**West Nile Virus Perinatal Transmission**	Hinckley AF et al, 2007	Transmission of West Nile Virus Through Human Breast Milk Seems to Be Rare, 2007	• Of 10 reported instances since 2003 of maternal or infant West Nile virus illness while breastfeeding, transmission of WNV through human milk could neither be ruled out nor confirmed for 5 cases; in 5 others, serologic tests indicated no vertical transmission. Transmission of WNV through breastfeeding seems to be rare, but more information is needed.	Hinckley AF, O'Leary DR, Hayes EB. Transmission of West Nile Virus Through Human Breast Milk Seems to Be Rare. *Pediatrics*. 2007;119(3):e666-71 http://www.ncbi.nlm.nih.gov/pubmed/17332186
57.	**West Nile Virus Perinatal Transmission**	Pridjian G et al, 2014	A Prospective Study of Pregnancy and Newborn Outcomes in Mothers with West Nile Virus	• 28 infected mothers and 26 non-infected mothers enrolled between 2005-2008 using the CDC WNV registry. • There were no differences I pregnancy and delivery characteristics except that infected mothers had a higher incidence of febrile illnesses and used more medications. • One mother with WNV had a perinatal loss due to acute abruption placenta at 31 weeks gestation (3 weeks post WNV meningitis).	Gabriella Pridjian, Patricia Sirois, Robert McRae, et al. 388: A Prospective Study of Pregnancy and Newborn

			Illness During Pregnancy	• No child had overt clinical symptoms at delivery • Rate of congenital malformations were similar • Only 2 children out of 17 who had the Bayley-III assessments performed in the WNV maternal group, performed below age expectations in one or more domains,	Outcomes in Mothers with West Nile Virus Illness During Pregnancy. [Poster Session]. *AJOG*. 2014;S197 http://www.ajog.org/article/S0002-9378(13)01486-5/pdf
58.	**West Nile Virus Perinatal Transmission**	Sirois P et al, 2014	Developmental Outcomes in Young Children Born to Mothers with West Nile Illness during Pregnancy	• Mother and child participants identified using national surveillance registry for WNV (O'Leary 2006) to examine relationship between maternal WNV during pregnancy and developmental outcomes at age 3 years • Total of 11 children completed follow-up; of these 11 children IgM levels at the time of delivery were negative for WNV congenital infection • The Bayley Scales of Infant and Toddler Development-3rd edition were administered to the children at 3 years of age • The Bayley-III assessed cognitive, language, motor, social-emotional, and adaptive behavior. • Only one child was in the mildly delayed range in the adaptive behavior domain but at age level for all other domains. • As a group, the children's performance was at or above age level in all domains of the Bayley-III.	Sirois PA, Pridjian G, McRae S, et al. Developmental Outcomes in Young Children Born to Mothers with West Nile Illness during Pregnancy. *Birth Defects Res A Clin Mol Teratol*. 2014;100(10):792-6. doi: 10.1002/bdra.23297
59.	**Infant and Child**	Fleming-Dutra KE, et al. 2016	Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with	• Updated Recommendations for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection o Testing of infants with possible congenital Zika virus infection who were born to mothers who traveled to or resided in areas affected by Zika virus during pregnancy should be guided by 1) whether the infant had microcephaly or intracranial	Fleming-Dutra KE, Nelson JM, Fischer M, et al. Update: Interim Guidelines for Health Care Providers Caring

			Possible Zika Virus Infection — United States, February 2016	calcifications detected prenatally or at birth and 2) the mother's Zika virus testing results. o The evaluation of infants with microcephaly or intracranial calcifications or infants whose mothers have positive or inconclusive test results for Zika virus infection remains the same o Infants without microcephaly or intracranial calcifications whose mothers have negative Zika virus test results or who were not tested for Zika virus should receive routine care • Evaluation and Management of Infants and Children Aged <18 Years with Possible Acute Zika Virus Disease o Acute Zika virus disease should be suspected in an infant or child aged <18 years who 1) traveled to or resided in an affected area within the past 2 weeks and 2) has two or more of the following manifestations: fever, rash, conjunctivitis, or arthralgia. o Acute Zika virus disease should also be suspected in an infant in the first 2 weeks of life 1) whose mother traveled to or resided in an affected area within 2 weeks of delivery and 2) who has two or more of the following manifestations: fever, rash, conjunctivitis, or arthralgia. • Recommended Zika virus laboratory testing for infants and children, recommended clinical evaluation and laboratory testing for infants with possible congenital Zika virus infection, and recommended long-term follow-up for infants with possible congenital Zika virus infection are provided in detail. • Guidelines for Breastfeeding for Mothers with Zika Virus Infection o Current evidence suggests that the benefits of breastfeeding outweigh the theoretical risks of Zika virus transmission through breast milk. • Prevention of Zika Virus Infection in Infants and Children o Mosquito bite prevention includes using air conditioning or window and door screens when indoors, wearing long-sleeved	for Infants and Children with Possible Zika Virus Infection — United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65(Early Release):1–6. DOI: http://dx.doi.org/10.15585/mmwr.mm6507e1er

				shirts and long pants, using permethrin-treated clothing and gear, and using insect repellents. o Most Environmental Protection Agency–registered insect repellents can be used to protect children aged ≥2 months against mosquito bites. o Oil of lemon eucalyptus should not be used in children aged <3 years (http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/protection-against-mosquitoes-ticks-other-arthropods). o Mosquito netting can be used to cover infants in carriers, strollers, or cribs to protect them from mosquito bites. Information on the safe use of insect repellents in children is available at https://www.epa.gov/insect-repellents/using-insect-repellents-safely-and-effectively. o Persons with Zika virus infection should take steps to prevent mosquito bites for at least the first week of illness to decrease the risk for human-to-mosquito-to-human transmission.	
60.	**Sexual Transmission**	Foy et al, 2011	Probable Non-Vector-borne Trans-mission of Zika Virus, Colorado, USA	• In 2008, two American scientists reported being bitten repeatedly by *Aedes* spp. mosquitoes in Senegal (both had also been vaccinated with the Yellow Fever Vaccine prior to travel). • Both patients became ill 6-9 days after their return to Colorado, US. • 6 days after Scientist # 1 returned he noted swollen ankles, maculopapular rash, fatigue and headache. 7 days after his return he developed symptoms of prostatitis (perineal pain and mild dysuria); 9 days after his return, signs of hematospermia were noted, which lasted for a total of 5 days. • Similar typical clinical symptoms occurred in his wife (who had not traveled to an endemic area) on day 9 of his return (after they noticed the hematospermia) and continued for 3 days. On day 4 of the wife's symptoms, she developed maculopapular rash and aphthous ulcer insider her lip. • Acute-phase and convalescent phase paired serum specimens were tested for all 3 patients; RT-PCR was negative for all 3 patients as was	Foy BD, Kobylinski KC, Foy JLC, et al. Probable non–vector-borne transmission of Zika virus, Colorado, USA. *Emerg Infect Dis*. 2011; epub. doi: 10.3201/eid1705.101939

				virus isolation. • Both scientists did, however, have hemagglutination inhibition antibody titers and virus neutralizing titers highly elevated above background levels for ZIKV and yellow fever virus (YFV); these results were confirmed with complement fixation tests against ZIKVC and YFV antigens. • Hemagglutination inhibition, complement fixation, and virus neutralizing titers against ZIKV alone developed only in the convalescent-phase sample of the wife of scientist #1. *Note- no semen samples were reported to be tested.	
61.	**Sexual Transmission**	Musso et al, 2015	Potential Sexual Transmission of Zika Virus	• December 2013, during the French Polynesian, South Pacific ZIKV outbreak, a 44 year old male in Tahiti presented for symptoms of ZIKV infection of which he had 2 episodes (8 weeks apart, each lasting 3 and 7 days, respectively) prior to seeking treatment. He sought treatment 2 weeks after recovering from the second episode after noting signs of hematospermia. • RT-PCR was positive for ZIKAV in semen and negative in blood in repeated samples. • It is suggested that the replication may have occurred in the genital tract and that transmission via sexual intercourse is possible.	Musso D, Roche C, Robin E, Nhan T. Potential sexual transmission of Zika virus. *Emerg Infect Dis*. 2015; 21(2):359-361. http://dx.doi.org/10.3201/eid2102.141363
62.	**Sexual Transmission**	Barzon et al, 2016	Isolation of infectious Zika virus from saliva and prolonged viral RNA shedding in a traveller returning from the Dominican Republic to Italy, January 2016	• 20+ year old female developed febrile illness after returning to Italy after a 2 week stay in the Dominican Republic in January 2016. • ZIKV was isolated from a saliva sample collected on day 6 after symptom onset. • Real time RT-PCR for Zika virus (ZIKV) was positive in plasma, urine, and saliva, with estimated ZIKV RNA loads of 30 copies/mL; 0.5x106 copies/mL; and 3x106 copies/mL, respectively; antibodies and RT-PCR for DENV, CHIKV were negative • Real-time RT-PCR testing of follow-up blood, urine, and saliva samples demonstrated persistent shedding of ZIKV RNA in saliva and urine for up to 29 days after symptom onset, while viral RNA was detectable in plasma up to day 10 after symptom onset.	Barzon L, Pacenti M, Berto A, Sinigaglia A, et al. Isolation of infectious Zika virus from saliva and prolonged viral RNA shedding in a traveller returning from the Dominican

				• ZIKV RNA load in saliva and urine was higher than in blood also in follow-up samples. • Anti-ZIKV IgM and IgG antibodies appeared on days 7 and 10, respectively	Republic to Italy, January 2016. Euro Surveill. 2016;21(10):pii=30159. DOI: http://dx.doi.org/10.2807/1560-7917
63.	**Sexual Transmission**	Deckard DT et al, 2016	Male-to-Male Sexual Transmission of Zika Virus — Texas, January 2016. MMWR	• First report of transmission of Zika virus from an infected man to a sex partner through anal sex • In January 2016, 2 days after returning to Dallas, Texas, from a 1-week visit to Venezuela, patient A developed subjective fever, pruritic rash on his upper body and face, and conjunctivitis lasting 3 days. • Both 1 day before and 1 day after his symptom onset (Day 0), patient A had condomless anal sex with patient B. • One week after intercourse, patient B developed a subjective fever, myalgia, headache, lethargy, and malaise, pruritic rash on his torso and arms, small joint arthritis of his hands and feet, and conjunctivitis. All symptoms resolved after 1 week. • 4 days after patient B's illness onset, serum was taken; and from both patients A and B on Day 14 (14 and 7 days after respective illness onsets). • On Day 24, semen, urine, and saliva specimens were collected from both patients (24 and 17 days after respective illness onsets). • Patient A's serum from 14 days after illness onset and patient B's serum from 4 days after illness onset contained no detectable Zika virus RNA using reverse transcription polymerase chain reaction (RT-PCR) testing. • Sera from both patients demonstrated positive immunoglobulin M (IgM) responses by capture ELISA for Zika virus and dengue virus • Plaque-reduction neutralization tests indicated that patient A had been infected with Zika virus, dengue virus serotype 1, or both, but that patient B had been infected only with Zika virus.	Deckard DT, Chung WM, Brooks JT, et al. Male-to-Male Sexual Transmission of Zika Virus — Texas, January 2016. MMWR Morb Mortal Wkly Rep 2016;65:372–374. DOI: http://dx.doi.org/10.15585/mmwr.mm6514a3

				• Urine and saliva specimens collected from patients A and B at 24 and 17 days after respective illness onsets had no detectable Zika virus by RT-PCR. • Semen specimens collected at 24 and 17 days from each man were tested for Zika virus by RT-PCR both by CDC and DCHHS using the same two sets of primers; At CDC, neither sample had detectable Zika virus with either primer set after 37 cycles; At DCHHS, which pretreated the thawed semen samples with dithiothreitol (used to induce liquefaction of viscous specimens and potentially increase detection of RT-PCR targets), patient B's specimen was negative. Patient A's specimen had Zika virus detected at 35 cycles with one primer set but produced no signal after 37 cycles with the other primer set. Patient A's semen results were thus deemed equivocal.	
64.	**Sexual Transmission**	Hills S. et al, 2016	Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission — Continental United States, 2016	• CDC reports that currently, all reported cases of sexual transmission of Zika virus have been from symptomatic male partners. • During February 6–22, 2016, two confirmed and four probable cases of sexual transmission were reported • Sexual contact included condomless vaginal intercourse and took place when the male partner was symptomatic or shortly after his symptoms had resolved. • Health care providers should now consider any person who has had condomless sex (i.e., vaginal intercourse, anal intercourse, or fellatio) with a male partner who has traveled to an area of ongoing Zika virus transmission and who has had symptoms of Zika virus disease during travel or within 2 weeks of return as potentially exposed. • Routine testing of men who have traveled for the purpose of assessing risk for sexual transmission is not recommended • Men who reside in or have traveled to an area of ongoing Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sex with their pregnant partner for the duration of the pregnancy • The length of time that virus might persist in semen is unknown. A recent report described detection of Zika virus RNA in semen by RT-	Hills SL, Russell K, Hennessey 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;65:215–216. DOI: http://dx.doi.org/10.15585/mmwr.mm6508e2

				PCR as long as 62 days after illness onset; however, infectious virus was not cultured from semen	
65.	**Sexual Transmission**	Mansuy JM et al, 2016	Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen?	• 32-year old male who presented with clinical symptoms of arbovirus infection 2 days after returning to France from Brazil and French Guyana • RT-PCR revealed ZIKV with no evidence of either CHIKV or DENV • He completely recovered a few days after • Further blood, urine and semen samples were collected 2 weeks after diagnosis • RNA virus loads were 2.8 log10 copies per mL in plasma, 3.1 in urine, and 8.6 in semen • The viral load was 100,000 times that of his blood or urine more than 2 weeks after symptom onset. • It was also noted that the ZIKV could replicate in African green monkey cells and the viral load increased by 4 log 10 in culture fluid on days 3 and 8 after inoculation • The duration of excretion is unknown but the virus may persist for many months	Mansuy JM, Dutertre M, Mengelle C, et al. Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen? *Lancet Infect Dis* [Correspondence]. 2016: March 3 [Epub ahead of print] doi: 10.1016/S1473-3099(16)00138-9
66.	**Sexual Transmission**	Oster A et al, 2016	Interim Guidelines for Prevention of Sexual Transmission of Zika Virus- US, 2016.	• Recommendations for men and their pregnant partners: o Men who reside in or have traveled to an area of active Zika virus transmission should abstain from sexual activity or consistently and correctly use condoms during sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for the duration of the pregnancy. o Pregnant women should discuss their male partner's potential exposures to mosquitoes and history of Zika-like illness • Recommendations for men and their non-pregnant sex partners o Men who reside in or have traveled to an area of active Zika virus transmission consider abstaining from sexual activity or using condoms consistently and correctly during sex.	Oster A, Brooks J, Stryker E, et al. Interim Guidelines for Prevention of Sexual Transmission of Zika Virus- US, 2016. *MMWR Morb Mortal Wkly Rep.* 2016;65:1-2 http://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm

				o Most infections are asymptomatic, and when illness does occur, it is usually mild with symptoms lasting from several days to a week; severe disease requiring hospitalization is uncommon. • Testing of men for the purpose of assessing risk for sexual transmission is not recommended due to limited understanding of the incidence and duration of shedding in the male genitourinary tract.	6505e1er.pdf
67.	**Laboratory**	Lanciotti et al, 2008	Genetic and Serologic Properties Zika Virus Associated Epidemic, Yap State, Micronesia, 2007, August 2008	• Methods and results of serologic testing, real time RT-PCR, and nucleic acid sequencing and phylogenetic analysis associated with the 2007 Zika epidemic in Yap state and Federated States of Micronesia were reported. • Serologic analysis was performed for IgG and IgM and PRNTs of all acute- and convalescent-phase paired specimens obtained during the epidemic. Specimens were divided into primary and secondary infections on the basis of antibody testing results. Most patient specimens from the Yap epidemic tested were secondary flavivirus infections. Serologic data indicated that ZIKV-infected patients can be positive in an IgM assay for DENVs, particularly if ZIKV is a secondary flavivirus infection. If ZIKV is the first flavivirus encountered, then cross-reactivity was found to be minimal. The PRNT result from one patient suggested previous yellow fever vaccination. • Real-time RT-PCR of 157 specimens was performed, of which 17 tested positive, 10 were equivocal, and 130 tested negative. Most (15 of 17) of the ZIKV-positive samples were from specimens collected <3 days after disease onset. • Nucleic Acid Sequence and Phylogenetic Analysis was performed of RT-PCR positive specimens.	Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. *Emerg Infect Dis.*2008; 14(8). doi: 10.3201/eid1408.080287
68.	**Laboratory**	Hirayama et al, 2012	Detection of Dengue Virus Genome in Urine by Real-Time Reverse Transcriptase PCR	• Serum and urine samples were collected from 53 dengue (DENV) patients in Japan from 2006-2008; median age 30. • The detection rates of 50% or higher of DENV were evident between days 6 to 16 for urine samples. • The detection rates of 50% or higher of DENV in serum samples were evident days 0 to 7.	Hirayama T, Yasutaka Mizuno Y, Takeshita N, et al. Detection of Dengue Virus Genome in Urine

				• Nucleotide sequences of PCR products were identical between urine and serum samples. • It is recommended that urine samples with RT-PCR are useful mainly as a supplemental test in the convalescent stages of DENV infection.	by Real-Time Reverse Transcriptase PCR: a Laboratory Diagnostic Method Useful after Disappearance of the Genome in Serum. *JCM*. 2012;50(6): 2047-52. doi:10.1128/JCM.06557-11
69.	**Laboratory**	Gourinat et al, 2015	Detection of Zika Virus in Urine	• Serum and urine samples were obtained from 6 patients who showed the same symptoms of cutaneous maculopapular rash of the trunk and extremities, and mild leukopenia and thrombocytopenia. • ZIKAV RNA was detected in all 6 urine samples. • For all cases with sequential specimens, ZIKAV RNA was detected in the urine ≤15 days (range 10 days to >20 days) after onset of symptoms, which was >7 days after it was not detected in serum samples; In serum samples, ZIKV was detected in patient serum until a rash was observed/ days 2-3 after disease onset.	Gourinat A, O'Connor O, Calvez E, Goarant C. Detection of Zika Virus in Urine. *Emerg Infect Dis*. 2015; 21(1): 84–86. doi: 10.3201/eid2101.140894
70.	**Laboratory**	Musso et al, 2015	Detection of Zika virus in saliva, April 2015	• During the French Polynesian Zika Outbreak, from October 2013 to March 2014, several patients observed to present with symptoms of acute phase Zika fever were tested negative in blood by ZIKV real-time PCR (RT-PCR). • Use of saliva was considered as an alternative sample for routine ZIKV RNA detection. • Over a 6 month period, 1,067 samples (saliva only, blood only, or both samples) were collected from 855 patients presenting with symptoms	Musso D, Roche C, Nhan TX, Robin E. Detection of Zika virus in saliva. *J Clin Virol*. 2015;68:53-5. doi: 10.1016/j.jcv.2015.04.021

				of Zika illness. • ZIKV was more frequently detected in saliva compared to blood. • For the 182 patients with both samples collected, tests were positive for 35 (19.2%) in saliva while negative in blood and tests were positive for 16 (8.8%) in blood while negative in saliva. • Conclusion: The use of saliva sample increased the rate of molecular detection of ZIKV at the acute phase of the disease but did not enlarge the window of detection of ZIKV RNA. Saliva was of particular interest when blood was difficult to collect (children and neonates especially).	
71.	**Laboratory**	Lustig Y et al, 2016	Detection of Zika virus RNA in whole blood of imported Zika virus disease cases up to 2 months after symptom onset, Israel, December 2015 to April 2016	• A total of six Israeli travelers with symptoms of ZVD had serum, whole-blood and urine samples examined; follow-up serum, urine and whole blood specimens were only available for five patients. • qRT-PCR was positive for only one of six serum samples, which was drawn 3 days post-symptom onset. The negative 5 serum samples were drawn 5 days post-symptom onset. • Of five samples tested for Zika virus IgM, four were IgM positive, including three which were also IgG positive. • Urine was positive in three samples obtained from three patients 5 to 26 days post-symptom onset; a second urine sample collected 46 days after onset was negative. • Five patients with whole blood examined, tested positive 5 to 58 days post-symptom onset • Overall, whole-blood samples were positive for as late as 2 months (58 days) post-symptom onset, which was longer than for urine (26 days) and serum (3 days). • The authors suggest that these findings suggest the utility of whole blood in Zika infection diagnosis.	Lustig Y, Mendelson E, Paran N, Melamed S, Schwartz E. Detection of Zika virus RNA in whole blood of imported Zika virus disease cases up to 2 months after symptom onset, Israel, December 2015 to April 2016. Euro Surveill. 2016 Jun 30;21(26). doi: 10.2807/1560-7917.ES.2016.21.26.30269.