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Review article

Zika Virus: a Review from the Virus Basics to Proposed Management Strategies

Lorenzo Zammarchi[1,2], Michele Spinicci[1] and Alessandro Bartoloni[1,2]

[1] Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze, Florence, Italy.
[2] SOD Malattie Infettive e Tropicali, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

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Abstract. This review aims to summarize the body of knowledge available on Zika virus to date. A comprehensive review of the scientific literature on Zika virus was performed with the aim to stress relevant aspects for healthcare professionals in the non-endemic areas. For several years, the Zika virus infection was considered an extremely rare exotic disease with poor clinical relevance. However, Zika virus has recently gained the attention of the scientific community and public opinion since the virus spread to the Pacific islands and the South America in an unprecedented epidemic, and additionally due to the definitive evidence that the infection could be complicated by Guillain-Barré syndrome, passed through vertical transmission, and result in central nervous system abnormalities (including microcephaly) of the fetus. Studies and scientific evidence on the complications associated with Zika virus infection are growing day by day. It is advisable that the healthcare professionals working in non-endemic areas maintain full awareness on this issue in order to practice proper management of the imported cases of Zika virus infection.

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Correspondence to: Alessandro Bartoloni. Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze, Florence, Italy and SOD Malattie Infettive e Tropicali, Azienda Ospedaliero Universitaria Careggi, Florence, Italy. E-mail: alessandro.bartoloni@unifi.it

Introduction. For about 60 years after its first isolation, which occurred in 1947 from a rhesus monkey in the Zika Forest, Uganda,[1] the Zika virus (ZIKV) infection has been considered responsible for an extremely rare exotic disease of poor clinical relevance and limited public health importance. However, since the virus spread to the Pacific islands and the South America, causing an unprecedented epidemic, it has received the attention of the scientific community along with public opinion, due to the definitive evidence that the infection is associated with Guillain-Barré syndrome (GBS) and, when contracted during pregnancy, with microcephaly and other abnormalities of the central nervous system of the fetus.[2]

Etiologic Agent. ZIKV is an arbovirus (arthropod borne viruses), and it is transmitted by mosquitoes of the genus *Aedes*. It belongs to the family Flaviviridae, genus *Flavivirus*, with little genomic divergence from other viruses of the same genus.[3] The genome of ZIKV consists of a single-stranded positive sense RNA molecule of 10794 kb in length, and a single central open reading frame encoding for a polyprotein, between two non-coding regions.[4] The polyprotein is cleaved into a capsid protein, a precursor of the membrane protein, a protein for the envelope, and seven non-structural proteins.[4] Based on the sequencing of the entire genome, two main lineages were identified, i.e. the African lineage, further divided into two groups (clusters Uganda and Nigeria) and

the Asian lineage, recently also called Asian/American.[3] Most of the strains belonging to the African lineage were isolated from enzootic vectors, whereas the Asian lineage has been associated with the major human epidemics reported until now.[3] The strains recently isolated in the Americas (Brazil, Puerto Rico, Haiti, Guatemala, Suriname) show a rapid and wide genetic divergence, probably linked to the spread of the virus into an immunologically naïve population.[3] Some authors suggest that the high rate of complications of ZIKV infection not described previously (namely microcephaly and GBS), could be due to the phenotypic variations of new strains that have originated from the Asian lineage. For example, the new strains could induce a higher viremia, fostering the transplacental transmission and the generation of the human reservoir, or they could manifest a greater neurotropism.[3]

Life Cycle, Reservoirs and Transmission Route. ZIKV infection is mainly transmitted through a vectorial route by the bite of mosquitoes belonging to the genus *Aedes*.[3] Before it spread to the Pacific Islands and the Americas, ZIKV was maintained in nature through a sylvatic cycle, which is probably still the case in Africa.[5] In Africa, enzootic transmission is prevalent; non-human primates are the main reservoirs (maybe with other vertebrates such as small mammals, birds, and reptiles) and the vectors are various species of mosquitoes that proliferate preferably in forests, such as *Ae. furcifer*, *Ae. luteocephalus*, *Ae. africanus*, *Ae. vittatus*, *Ae. taylori*, *Ae. dalzieli*, *Ae. hirsutus*, *Ae. metallicus*, *Ae. unilinaetus*, *Mansonia uniformis*, *Anopheles coustani* and *Culex perfuscus*.[5,6] Human cases in this setting are sporadic. Conversely, the urban cycle has sustained the epidemics reported in Micronesia in 2007, in French Polynesia in 2013-2014, as well as the current outbreak in the Americas.[7-9] In these cases, humans are the main reservoir, whereas the vectors are different mosquitoes of the genus *Aedes*, such as *Ae. hensilli*, *Ae. polynesiensis* and *Ae. aegypti* that have had (or still have) a role in the epidemics in Micronesia,[10] French Polynesia[11] and the Americas,[6] respectively. Furthermore, there is laboratory evidence that *Ae. albopictus* (including the Italian strain) can be a competent vector for ZIKV,[12,13] though less effective than *Ae. aegypti*.[13,14] To date, *Ae. albopictus* has been only suspected to have played a role in the epidemic occurred in Gabon in 2007 when the virus was detected both in the serum of febrile individuals and in mosquitoes of this species.[15] In that case, the ZIKV strain belonged to the African lineage.[15]

A growing body of evidence indicates that the virus can be transmitted during pregnancy through the placenta and within the perinatal period.[16,17] Indeed, viral RNA was detected by the Polymerase Chain Reaction (PCR) in the amniotic fluid, the fetal tissues, and the central nervous system of newborns from women who contracted the infection in pregnancy.[17,18] There are a number of case reports demonstrating the possibility of sexual transmission from an infected male to his partners (both female and male), both in the case of the symptomatic and asymptomatic disease.[19-21] The virus was detected in the sperm up to 24 days after infection by the viral isolation technique and after 188 days by PCR.[22] Recently, the first case of female-to-male sexual transmission of ZIKV was reported in the United States,[23] and ZIKV RNA has been detected in vaginal fluids 3 days after symptom onset, and in one case, in cervical mucus up to 11 days after symptom onset.[24] Moreover, the virus can potentially be transmitted through blood transfusions and other substances of human origin (SoHO).[25] There are also a few cases due to laboratory accidents,[26] and a single report of suspected transmission due to a monkey bite.[27] Aside from serum, the virus has also been isolated from urine, saliva, breast milk and semen; although the possibility of transmission through saliva, breast milk, and urine has not been demonstrated to date.[28-31]

Epidemiology. ZIKV was detected for the first time in the blood of a rhesus monkey in 1947 at the Yellow Fever Research Institute in Entebbe, Uganda, and again in the following year, in the vector *Ae. africanus*.[1] The diagnosis of the first human case dates back to 1954, in Nigeria, during the investigation of a jaundice outbreak due to Yellow fever.[32] After its discovery, the circulation among humans of ZIKV in various areas of Africa and Asia was confirmed by a few case reports and some seroprevalence studies.[7,33] The first large outbreak was described in 2007, in the Federal State of Yap islands in Micronesia, where ZIKV infected about 5,000 people, corresponding to 75% of the population.[34] In Thailand, East Malaysia, Cambodia, the Philippines and Indonesia, sporadic

cases were reported in the following years.[33] Between October 2013 and April 2014, a second large outbreak affected French Polynesia, where it is estimated that 32,000 people were infected (11% of the population).[7] Subsequently, the virus spread in many other Pacific Islands such as the Cook Islands, Easter Island and New Caledonia, the Solomon Islands and Vanuatu.[33] At the beginning of 2015, ZIKV reached the Americas for the first time, where it was first reported in Brazil's northeastern State of Rio Grande do Norte,[9] and in a traveller returning to Italy who visited Bahia in the same period.[35] Briefly, the virus has spread throughout most of the Brazilian States, causing, as of February 2016, between 500,000 and 1,500,000 infections, according to data from the Brazilian Ministry of Health.[36] Since October 2015, Colombia also began to report indigenous cases, followed by many other states of the Americas.[37] Currently the World Health Organization indicates the presence of a continuous vectorial transmission in 60 countries and territories, including most of the states of Central and South America, many countries in South East Asia, Oceania and the Pacific and, with regard to Africa, Cape Verde and more recently, Guinea Bissau.[2,38] In July 2016, several autochthonous cases were reported in Florida, United States.[39] The list of countries with current autochthonous transmission of ZIKV is available on the website of the European Centre for Disease Prevention and Control: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx.

The risk to be infected while travelling seems quite small. According to data from the CDC, in USA among 3,335 pregnant women who moved to- or lived in areas at risk and were tested for ZIKV, only 0.8% tested positive; a positive result occurring in 2.9% among those who had at least a typical symptom of ZIKV, and 0.3% of those which remained asymptomatic.[40]

Clinical Manifestations and Pathogenesis of Complications. The infection is asymptomatic in about 80% of cases.[8] The incubation period in symptomatic cases is not precisely known. According to a systematic review, the median incubation period is 5.9 days and 95% of individuals develops symptoms 11.2 days after the exposure.[41] According to the European Centre for Disease Control and Prevention (ECDC) case definition, exposure in an area with transmission of ZIKV within two weeks prior to the onset of symptoms is considered epidemiological criteria for diagnosis, as the incubation period is likely less than 14 days.[42] The infection acquired vectorially or by sexual contact has, in almost all cases, a benign course without complications leading to resolution of symptoms within a period of about two weeks. The most common manifestation (90% of cases) is a rash, typically macular or maculopapular, often itchy and with centrifugal evolution (from the trunk to the extremities), that generally lasts 4-5 days (range: 2-14 days).[7,8,33] In about 65-70% of cases, the rash may be preceded by 1-4 days of fatigue and fever (generally lower than 38 degrees) for maximum 7 days.[7,43] The third most frequent symptom is arthralgia (65% of cases), eventually associated in 20-45% of cases with periarticular edema (hands and feet, and less frequently knees and wrists), which generally persist for a week (up to a month).[7] Bilateral, not purulent conjunctival injection may occur in approximately 55-60% of cases, and it typically resolves in 1-2 weeks.[7,8] Other manifestations include headache, myalgia, and retro-orbital ocular pain. In a case series of Brazilian pregnant women with ZIKV infection, localized or generalized lymphadenopathy was found to be a relatively common clinical manifestation (40% of cases), whereas it was reported in only 15% of cases during the French Polynesia outbreak.[7]

Some authors speculate that the high phenotypic variation rate of the strains belonging to the Asian lineage isolated in the Americas could result in infections characterized by a greater neurotropism or a higher viremia, thus fostering the transplacental transmission.[3] Two different mechanisms were hypothesized to explain the pathogenesis of neurological complications and the congenital infection: a direct viral damage and an immune-mediated mechanism.[44] Most of the studies conducted so far have investigated the former. Studies in animal models (rat) showed that ZIKV is extremely neurotropic [45] and that it could be transmitted through the placenta, inducing growth retardation, fetal death, placental damage, apoptosis of neural progenitor cells, and impaired neural proliferation and development in affected fetus.[46-48] Concerning the immune-mediated hypothesis, only slight differences in cytokine

levels between acute and convalescent samples have been observed in a small cohort of patients.[49] Another interesting *in vitro* observation is that plasma immune to virus (DENV) was able to enhance ZIKV infection probably through a mechanism of antibody dependent enhancement (ADE).[50] According to the ADE mechanism, which has been hypothesized for DENV, antibodies generated during a primary infection with DENV will not be of sufficient concentration or avidity to neutralize a secondary infection with DENV of a different serotype, however, they might still opsonize the secondary virus and thus drive higher viral loads.[50] This observation suggests that subjects with previous DENV immunity could have more severe ZIKV clinical manifestations or increased risk of transplacental transmission compared with subjects without previous DENV infection.

The correlation between ZIKV infection and GBS was observed for the first time in 2013-2014 during the ZIKV outbreak in French Polynesia. The outbreak registered 42 cases in 4 months, compared to an average of 5 cases per year before 2013.[29] A study, reporting data from French Polynesia epidemic, showed that the risk of developing GBS after ZIKV infection is around 2.4 per 10,000 infections Zika virus, similar to the risk following a *Campylobacter jejuni* infection.[43] The appearance of GBS occurred after a period ranging from 2 to 23 days (median 6 days) after the onset of the symptoms of infection.[7] The typical electromyography pattern found in these patients was characterized by acute motor axonal neuropathy, without the ganglioside antibodies that are characteristic of this condition.[51] At present, in addition to French Polynesia, 12 other countries affected by a ZIKV epidemic reported at least one case of GBS in patients with recent infection, and 8 reported a significant increase compared to previous years.[52] In particular, in Brazil from January to November 2015 1,708 cases were registered, corresponding to an increase which varied among the states ranging from +526.7% (Alagoas) to +60.9% (Rio de Janeiro).[53]

The correlation between ZIKV and microcephaly and other damages due to congenital infection was first observed in Brazil. In October 2015, about seven months after the identification of the first cases of ZIKV in the northeast of Brazil, the Ministry of Health of Brazil reported an unusual increase in cases of microcephaly in the states of Pernambuco, Paraiba and Rio Grande do Norte, with an evident geographical overlap with the epidemic of ZIKV.[54]

In November 2015, in the state of Paraiba, ZIKV RNA was detected in the amniotic fluid of two women whose fetus had an ultrasound diagnosis of microcephaly.[55] These findings induced the Brazilian Ministry of Health, the Centers for Disease Control (CDC), and the ECDC to issue specific alerts on the possible association of microcephaly and ZIKV infection.[56,57] On February 1, 2016, following the rise in cases of microcephaly and GBS in the areas of ZIKV spread, the WHO declared ZIKV a Public Health Emergency of International Concern.[58] An increase of 20-times in the frequency of microcephaly (20 cases per 10,000 live births) was found by comparing the historical statistics of this disorder in Brazil with those of 2015.[59] On the other hand, current incidence of microcephaly in Brazil could be partially overestimated due to a previous under-diagnosis bias and a new surveillance protocol, which may have a higher sensitivity in detecting cases.[59,60] Between October 2015 and June 30, 2016, Brazil reported 8,165 suspected cases of microcephaly and other nervous system disorders suggestive of congenital infection.[38] Of these, 1,638 are confirmed cases of microcephaly, 270 of which have been laboratory-confirmed for ZIKV infection.[38] An increase in cases of microcephaly has been found retrospectively also in French Polynesia after the epidemic of 2013-2014.[61] A retrospective study, based on a mathematical model and on data collected in French Polynesia, concluded that the risk of microcephaly was 1% for newborns of women who contracted the infection during the pregnancy, and the most dangerous period was the first trimester of gestation.[61] According to a second mathematical model built on Brazilian data, microcephaly could complicate from 0.88%-13.2% of pregnancies when the woman is infected in the first trimester.[62]

An observational study in Brazil reported fetal abnormalities in 29% (12 of 42) of the pregnant women infected with ZIKV, and in none of the 12 pregnant women who tested negative.[63] The anomalies included fetal deaths at 36 and 38 weeks of gestation (2 foetuses), intrauterine growth restriction (IUGR) with or without microcephaly (5), ventricular calcifications or

other disorders of the central nervous system (7 fetuses), abnormalities of the amniotic fluid volume, or the brain or umbilical artery flow (7 fetuses).[63]

In addition to Brazil and French Polynesia, several other countries reported autochthonous (Colombia, Cape Verde, El Salvador, French Guiana, Marshall Islands, Martinique, Panama, Puerto Rico) or imported cases (USA, Spain, Slovenia, all in women who had travelled in Central and South America) of malformations of the central nervous system due to ZIKV congenital infection.[38] Clinical data on infants with congenital infection are severe. A study conducted in the state of Pernambuco analysed 23 babies with microcephaly whose mothers reported symptoms compatible with ZIKV infection in the first or second trimester.[64] Seven underwent lumbar puncture with detection of IgM anti ZIKV in the cerebrospinal fluid. All the children had significant severe brain abnormalities noted at the CT scan, such as deficiency in brain development, brain calcifications (mainly in the corticomedullar junction), global hypogyration of the cerebral cortex, white matter abnormalities, and significant ventriculomegaly.[64] Moreover, almost a third of infants with microcephaly related to ZIKV congenital infection had ocular abnormalities, such as pigment accumulation in the retina and chorioretinal atrophy, abnormalities of the optic nerve, bilateral coloboma of the iris, and lens subluxation.[65]

Reports of other severe or life-threatening events are exceptional and almost always limited to patients with extreme age or comorbidities. Among those, there are 4 cases of neuroinvasive disease (a case of meningoencephalitis in an elderly,[66] a case of myelitis in a child,[67] two cases of encephalopathy[68]) and two fatal cases in patients with severe comorbidities (a child with sickle cell disease [69] and a man with alcoholism, systemic lupus erythematosus, and rheumatoid arthritis in chronic treatment with corticosteroids[70]).

Diagnosis. The diagnosis is based on serological and molecular tests, in addition to clinical and epidemiological criteria. The differential diagnosis of ZIKV infection may be challenging since signs and symptoms are nonspecific and mimic other infections and in particular other arbovirosis such as dengue and chikungunya which have similar clinical presentation and epidemiological distribution.[71,72] Moreover the accuracy of the serological tests for ZIKV, including the reference test of neutralization, is burdened by a high degree of cross-reactions with other flaviviruses.[19,72,73]

Furthermore, individuals with previous infections or immunizations by flavivirus may show the "antigenic original sin" phenomenon, i.e. they can present a specific antibody response to the virus which is responsible for the previous infection rather than to the current one.[74] A commercial ELISA test that uses the NS1 antigen of ZIKV shows good performance, including in terms of specificity.[75] IgG seroconversion occurs, on average, 9 days after the onset of symptoms, whereas the IgM may appear 4-5 days after the onset.[41]

With regard to the virological testing, PCR is the most used technique. PCR remains positive in serum in the first few days of symptoms (usually <7 days).[76] The persistence of viral RNA in saliva is similar, although some studies reported that it can last up to one month.[29] In urine, the persistence has been demonstrated up to 10-20 days after manifestation.[76,77] A recent study showed that ZIKV RNA may be detected by PCR in whole blood for a longer period than in serum and urine (up to 2 months post-symptom onset).[78] In one case, a pregnant woman (whose fetus had major malformations and congenital ZIKV infection) was still viremic at both 4 and 10 weeks after the onset of symptoms, suggesting a longer-lasting viremia in pregnant women.[79]

In the presence of a laboratory confirmed diagnosis during pregnancy and / or ultrasonographic evidence of fetal damage suggestive for fetal infection, PCR testing for ZIKV on amniotic fluid can be performed through amniocentesis.[17] Some experts recommended, similarly to other infections in the TORCH group, waiting until at least 21 weeks of gestation and 6 weeks after the onset of symptoms in the mother before performing amniocentesis.[80] The case definition of ZIKV according to the ECDC is reported in **Table 1**.

Clinical Management of Pregnant Women. Several institutions, like the CDC and ECDC, advise pregnant women against travelling to areas where the transmission of ZIKV is reported.[38,81] If the travel is indispensable, the woman should pay

attention to the prevention of insect bites, especially during the day, using icaridin or DEET

Table 1: Case definition for surveillance of Zika virus infection according to the European Centre for Disease Control and Prevention. Available at: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/patient-case-management/Pages/case-definition.aspx?preview=yes&pdf=yes#sthash.WAzTC7zm.dpuf

Classification	Probable case • A person meeting the clinical criteria and the epidemiological criteria. • A person meeting the laboratory criteria for a probable case Confirmed case • A person meeting the laboratory criteria for a confirmed case
Clinical criteria	A person presenting with a rash, with or without fever and at least 1 of the following signs and symptoms: • Arthralgia or • Myalgia or • Non-purulent conjunctivitis/hyperaemia
Laboratory criteria	Laboratory criteria for a probable case: • Detection of Zika specific IgM antibodies in serum Laboratory criteria for a confirmed case (at least 1 of the following): • Detection of Zika virus nucleic acid in a clinical specimen • Detection of Zika virus antigen in a clinical specimen • Isolation of Zika virus from a clinical specimen; • Detection of Zika virus specific IgM antibodies in serum sample(s) and confirmation by neutralization test • Seroconversion or four-fold increase in the titer of Zika specific antibodies in paired serum samples
Epidemiological criteria	• History of exposure in an area with transmission of Zika virus within two weeks prior to onset of symptoms or • Sexual contact with a male having been confirmed with a Zika virus infection in the past four weeks or • Sexual contact with a male who had been in an area with Zika virus transmission in the past four weeks • A list of Zika affected areas is kept updated on the ECDC website: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx

based products.[82] Both symptomatic and asymptomatic pregnant women exposed to the risk of infection (those returning from areas where transmission of Zika virus is known to occur or those who have had sex with males returning from areas at risk), should undergo a laboratory test for Zika.[83] Several flow charts for testing pregnant women have been proposed.[80,83-85] In general, the screening test to be used for pregnant should be selected according to the presence or absence of symptoms and the time elapsed since the potential exposure. Given the kinetics of the viro-immunological markers of infection, it is worthwhile to use both serological tests and PCR on serum, saliva, and urine if the tests are performed within one month from the onset of symptoms or since the last exposure.[76] After more than one month has passed, serology alone may be sufficient, though the long duration of viremia in pregnant women could support the use of PCR on serum even after a longer period has elapsed. It should be noted that the IgM might be negative even in the case of recent infection,[84] probably due to the "antigenic original sin" phenomenon.[74,86] In these cases, the diagnosis is based on positivity of IgG and PCR.[84] In the presence of a positive test for ZIKV, the woman should undergo an obstetric ultrasound follow-up every 3-4 weeks.[83] The option to perform amniocentesis in order to detect viral RNA by PCR,[83] mentioned previously, should be considered and discussed with the woman, even though data are not present on the sensitivity of this technique or on its prognostic value in case of a positive result (i.e. it's unknown if positive PCR necessarily lead to fetal and / or neonatal disease). Moreover, the presence of microcephaly cannot be accurately assessed with ultrasounds before the 3rd trimester of pregnancy.[80] Newborns from ZIKV infected women should undergo strict neonatology and pediatric controls, including serological and molecular testing for ZIKV.[83,84,87]

A pathological evaluation of fetal tissue specimens (e.g., placenta and umbilical cord) may be used to establish the presence of maternal Zika virus infection and can provide a definitive diagnosis for pregnant women with a ZIKV infection whose serology results were inconclusive due to possible cross reactions with other flaviviruses.[83]

Therapy and Vaccine. No therapies are available to date. The epidemiological and clinical experience obtained during the current outbreak makes the development of a ZIKV vaccine a global health priority. Promisingly, a recent study showed that a single immunization with a plasmid DNA vaccine or a purified inactivated virus vaccine could provide complete protection against ZIKV challenges in susceptible mice.[88] However, the achievement of a ZIKV vaccine for humans requires a better insight into ZIKV immunology and mechanisms of immune protection. For example, the development of a live-attenuated vaccine is inadvisable until the link between GBS and ZIKV will be elucidated and additional complications related to pre-existing flavivirus exposure should be deeply probed in order to develop an efficient and safe vaccine.[89]

Control Strategies in non-Endemic Area. Much of the world's tropical and sub-tropical regions are at risk for further ZIKV spread. In temperate zones, such as Europe, the emergence of autochthonous cases or small foci is possible anywhere competent vectors, basically, mosquitoes of *Aedes* genus, are present. In Europe, the presence of *Ae. aegypti* is currently limited to Madeira, the eastern coast of the Black Sea, and the Netherlands.[90] However, *Ae. albopictus* mosquitoes, which are proven competent vector for ZIKV,[13] albeit less efficient than *Ae. aegypti,* are widespread in several countries around the Mediterranean basin, especially in Italy.[90] *Ae. albopictus* was implicated in the autochthonous cases of dengue fever reported in 2010 in Croatia,[91] in 2010, 2013, and 2015 in France,[92-94] and of chikungunya in Italy in 2007,[95] in France in 2014,[96] and in Spain in 2015.[97] In non-endemic areas, the programs for arthropod-borne disease control, including ZIKV, have been based on the experience gained in the last decades in controlling the transmission of dengue and other arboviruses, and they are mainly focused on early detection and reporting of imported cases and vector control measures[98] in accordance with national strategies. For example, in Italy suspected cases must be notified to the Public Health Authorities within 12 hours during the period of activity of *Ae. albopictus* (from June to October) or within 24 hours during the rest of the year. In the period of vector activity, patients with suspected or confirmed diagnosis who are not hospitalized, should be advised to remain isolated at home.[85] Public health authorities should immediately activate rapid vector control measures as soon as imported cases are detected, in order to implement pest control methods around the residence of the index case and the other sites that infected patient visited. In France, where sporadic autochthonous cases of arboviruses have recurred periodically in the summer months since 2010, the response includes epidemiological and entomological door-to-door surveys around the index case residence in order to detect further infections by an active case finding, and to guide vector control measures (elimination of possible larval breeding sites, spraying of deltamethrin) in the outbreak areas.[92]

Despite that the main route of ZIKV transmission is via the *Aedes* mosquitoes, strong evidence has been demonstrated that ZIKV can be transmitted by sexual contact, including vaginal, anal and oral sexual intercourse. Based on the available knowledge, the CDC and WHO issued guidance papers on precautions to be kept: people returning from areas where local transmission of Zika virus is known should adopt safer sex practices or consider abstinence for at least 8 weeks upon return, and up to 6 months if the male partner is symptomatic; couples planning a pregnancy should wait for the same duration before attempting to conceive.[99] Men exposed to risks of infection should avoid unprotected sexual intercourse for the whole length of the gestation if their partner is pregnant.[99,100]

Moreover, a potential risk of ZIKV transmission through SoHO has been identified; competent authorities and healthcare professionals need to be vigilant regarding the risk of donor-derived ZIKV transmission. A document issued by the ECDC based on previous experiences, such as for West Nile Virus, is now available to support the implementation of national preparedness plans for the safety of SoHO, with respect to ZIKV infection, in both affected and non-affected area.[101]

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References:

1. Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. Trans R Soc Trop Med Hyg 1952;46:509-520. http://dx.doi.org/10.1016/0035-9203(52)90042-4
2. World Helath Organization. Situation Report. Zika virus, Microcephaly, Guillain Barré Syndrome, May 26, 2016. 2016.
3. Weaver SC, Costa F, Garcia-Blanco MA, Ko AI, Ribeiro GS, Saade G, Shi PY, Vasilakis N. Zika virus: History, emergence, biology, and prospects for control. Antiviral Res 2016;130:69-80. http://dx.doi.org/10.1016/j.antiviral.2016.03.010 PMid:26996139
4. Faye O, Freire CC, Iamarino A, de Oliveira JV, Diallo M, Zanotto PM, Sall AA. Molecular evolution of Zika virus during its emergence in the 20(th) century. PLoS Negl Trop Dis 2014;8:e2636.
5. Diallo D, Sall AA, Diagne CT, Faye O, Ba Y, Hanley KA, Buenemann M, Weaver SC, Diallo M. Zika virus emergence in mosquitoes in southeastern Senegal, 2011. PLoS One 2014;9:e109442.
6. Anderson KB, Thomas SJ, Endy TP. The Emergence of Zika Virus: A Narrative Review. Ann Intern Med 2016.
7. Mallet H, Vial A, Musso D. Bilan de l'épidémie à virus Zika en Polynésie Française 2013-2014. Bulletin d'information sanitaires, épidémiologiques et statistiques 2015.
8. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, Pretrick M, Marfel M, Holzbauer S, Dubray C, Guillaumot L, Griggs A, Bel M, Lambert AJ, Laven J, Kosoy O, Panella A, Biggerstaff BJ, Fischer M, Hayes EB. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med 2009;360:2536-2543. http://dx.doi.org/10.1056/NEJMoa0805715 PMid:19516034
9. Zanluca C, Melo VC, Mosimann AL, Santos GI, Santos CN, Luz K. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Oswaldo Cruz 2015;110:569-572. http://dx.doi.org/10.1590/0074-02760150192 PMid:26061233 PMCid:PMC4501423
10. Ledermann JP, Guillaumot L, Yug L, Saweyog SC, Tided M, Machieng P, Pretrick M, Marfel M, Griggs A, Bel M, Duffy MR, Hancock WT, Ho-Chen T, Powers AM. Aedes hensilli as a potential vector of Chikungunya and Zika viruses. PLoS Negl Trop Dis 2014;8:e3188.
11. Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Pacific area. Clin Microbiol Infect 2014;20:O595-596.
12. Wong PS, Li MZ, Chong CS, Ng LC, Tan CH. Aedes (Stegomyia) albopictus (Skuse): a potential vector of Zika virus in Singapore. PLoS Negl Trop Dis 2013;7:e2348.
13. Di Luca M, Severini F, Toma L, Boccolini D, Romi R, Remoli ME, Sabbatucci M, Rizzo C, Venturi G, Rezza G, Fortuna C. Experimental studies of susceptibility of Italian Aedes albopictus to Zika virus. Euro Surveill 2016;21.
14. Chouin-Carneiro T, Vega-Rua A, Vazeille M, Yebakima A, Girod R, Goindin D, Dupont-Rouzeyrol M, Lourenco-de-Oliveira R, Failloux AB. Differential Susceptibilities of Aedes aegypti and Aedes albopictus from the Americas to Zika Virus. PLoS Negl Trop Dis 2016;10:e0004543.
15. Grard G, Caron M, Mombo IM, Nkoghe D, Mboui Ondo S, Jiolle D, Fontenille D, Paupy C, Leroy EM. Zika virus in Gabon (Central Africa)--2007: a new threat from Aedes albopictus? PLoS Negl Trop Dis 2014;8:e2681.
16. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill 2014;19.
17. Calvet G, Aguiar RS, Melo AS, Sampaio SA, de Filippis I, Fabri A, Araujo ES, de Sequeira PC, de Mendonca MC, de Oliveira L, Tschoeke DA, Schrago CG, Thompson FL, Brasil P, Dos Santos FB, Nogueira RM, Tanuri A, de Filippis AM. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect Dis 2016.
18. Mlakar J, Korva M, Tul N, Popovic M, Poljsak-Prijatelj M, Mraz J, Kolenc M, Resman Rus K, Vesnaver Vipotnik T, Fabjan Vodusek V, Vizjak A, Pizem J, Petrovec M, Avsic Zupanc T. Zika Virus Associated with Microcephaly. N Engl J Med 2016;374:951-958. http://dx.doi.org/10.1056/NEJMoa1600651 PMid:26862926
19. Venturi G, Zammarchi L, Fortuna C, Remoli ME, Benedetti E, Fiorentini C, Trotta M, Rizzo C, Mantella A, Rezza G, Bartoloni A. An autochthonous case of Zika due to possible sexual transmission, Florence, Italy, 2014. Euro Surveill 2016;21.
20. Deckard DT, Chung WM, Brooks JT, Smith JC, Woldai S, Hennessey M, Kwit N, Mead P. Male-to-Male Sexual Transmission of Zika Virus - Texas, January 2016. MMWR Morb Mortal Wkly Rep 2016;65:372-374. http://dx.doi.org/10.15585/mmwr.mm6514a3 PMid:27078057
21. Fréour T, Mirallié S, Hubert B, Splingart C, Barrière P, Maquart M, Leparc-Goffart I. Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016. Euro Surveill 2016;21.
22. Nicastri E, Castilletti C, Liuzzi G, Iannetta M, Capobianchi M, Ippolito G. Persistent detection of Zika virus RNA in semen for six months after symptom onset in a traveller returning from Haiti to Italy, February 2016. Euro Surveill 2016;21(32):pii=30314. http://dx.doi.org/10.2807/1560-7917.ES.2016.21.32.30314
23. Davidson A, Slavinski S, Komoto K, Rakeman J, Weiss D. Suspected Female-to-Male Sexual Transmission of Zika Virus - New York City, 2016. MMWR Morb Mortal Wkly Rep 2016;65:716-717. http://dx.doi.org/10.15585/mmwr.mm6528e2 PMid:27442327
24. Prisant N, Bujan L, Benichou H, Hayot PH, Pavili L, Lurel S, Herrmann C, Janky E, Joguet G. Zika virus in the female genital tract. Lancet Infect Dis 2016.
25. Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, Shan Yan A, Cao-Lormeau VM, Broult J. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill 2014;19.
26. Filipe AR, Martins CM, Rocha H. Laboratory infection with Zika virus after vaccination against yellow fever. Arch Gesamte Virusforsch 1973;43:315-319. http://dx.doi.org/10.1007/BF01556147 PMid:4799154
27. Leung GH, Baird RW, Druce J, Anstey NM. ZIKA VIRUS INFECTION IN AUSTRALIA FOLLOWING A MONKEY BITE IN INDONESIA. Southeast Asian J Trop Med Public Health 2015;46:460-464.
28. Dupont-Rouzeyrol M, Biron A, O'Connor O, Huguon E, Descloux E. Infectious Zika viral particles in breastmilk. Lancet 2016;387:1051. http://dx.doi.org/10.1016/S0140-6736(16)00624-3
29. Barzon L, Pacenti M, Berto A, Sinigaglia A, Franchin E, Lavezzo E, Brugnaro P, Palu G. Isolation of infectious Zika virus from saliva and prolonged viral RNA shedding in a traveller returning from the Dominican Republic to Italy, January 2016. Euro Surveill 2016;21.
30. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis 2015;21:359-361. http://dx.doi.org/10.3201/eid2102.141363 PMid:25625872 PMCid:PMC4313657
31. Roze B, Najioullah F, Ferge JL, Apetse K, Brouste Y, Cesaire R, Fagour C, Fagour L, Hochedez P, Jeannin S, Joux J, Mehdaoui H, Valentino R, Signate A, Cabie A. Zika virus detection in urine from patients with Guillain-Barre syndrome on Martinique, January 2016. Euro Surveill 2016;21.
32. Macnamara FN. Zika virus: a report on three cases of human infection during an epidemic of jaundice in Nigeria. Trans R Soc Trop Med Hyg 1954;48:139-145. http://dx.doi.org/10.1016/0035-9203(54)90006-1
33. Plourde AR, Bloch EM. A Literature Review of Zika Virus. Emerg Infect Dis 2016;22.
34. Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, Lambert AJ, Johnson AJ, Stanfield SM, Duffy MR. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis 2008;14:1232-1239. http://dx.doi.org/10.3201/eid1408.080287 PMid:18680646 PMCid:PMC2600394
35. Zammarchi L, Tappe D, Fortuna C, Remoli ME, Gunther S, Venturi G, Bartoloni A, Schmidt-Chanasit J. Zika virus infection in a traveller returning to Europe from Brazil, March 2015. Euro Surveill 2015;20.
36. Zika virus infection: global update on epidemiology and potentially associated clinical manifestations. Wkly Epidemiol Rec 2016;91:73-81.
37. Zika virus outbreaks in the Americas. Wkly Epidemiol Rec 2015;90:609-610.
38. European Centre for Disease Prevention and Control. Zika virus disease epidemic. Rapid Risk Assessment. Seventh update. 8 July 2016. ECDC 2016.
39. McCarthy M. Four in Florida are infected with Zika from local mosquitoes. BMJ 2016;354:i4235.
40. Dasgupta S, Reagan-Steiner S, Goodenough D, Russell K, Tanner M, Lewis L, Petersen EE, Powers AM, Kniss K, Meaney-Delman D, Oduyebo T, O'Leary D, Chiu S, Talley P, Hennessey M, Hills S, Cohn A, Gregory C. Patterns in Zika Virus Testing and Infection, by Report of Symptoms and Pregnancy Status - United States, January 3-March 5, 2016. MMWR Morb Mortal Wkly Rep 2016;65:395-399. http://dx.doi.org/10.15585/mmwr.mm6515e1 PMid:27101541
41. Lessler J, Ott C, Carcelen A, Konikoff J, Williamson J, Bi Q, Kucirka L, Cummings D, Reichd N, Chaisson L. Times to key events in the course of Zika infection and their implications: a systematic review and pooled analysis. Bull World Health Organ 2016.

42. European Centre for Disease Prevention and Control. Proposed case definition for surveillance of Zika virus infection. ECDC Web Site 2016.
43. Waddell LA, Greig JD. Scoping Review of the Zika Virus Literature. PLoS One 2016;11:e0156376.
44. Adibi JJ, Marques ET, Jr., Cartus A, Beigi RH. Teratogenic effects of the Zika virus and the role of the placenta. Lancet 2016;387:1587-1590. http://dx.doi.org/10.1016/S0140-6736(16)00650-4
45. Lazear HM, Govero J, Smith AM, Platt DJ, Fernandez E, Miner JJ, Diamond MS. A Mouse Model of Zika Virus Pathogenesis. Cell Host Microbe 2016;19:720-730. http://dx.doi.org/10.1016/j.chom.2016.03.010 PMid:27066744
46. Cugola FR, Fernandes IR, Russo FB, Freitas BC, Dias JL, Guimaraes KP, Benazzato C, Almeida N, Pignatari GC, Romero S, Polonio CM, Cunha I, Freitas CL, Brandao WN, Rossato C, Andrade DG, Faria Dde P, Garcez AT, Buchpigel CA, Braconi CT, Mendes E, Sall AA, Zanotto PM, Peron JP, Muotri AR, Beltrao-Braga PC. The Brazilian Zika virus strain causes birth defects in experimental models. Nature 2016;534:267-271. http://dx.doi.org/10.1038/nature18296
47. Li C, Xu D, Ye Q, Hong S, Jiang Y, Liu X, Zhang N, Shi L, Qin CF, Xu Z. Zika Virus Disrupts Neural Progenitor Development and Leads to Microcephaly in Mice. Cell Stem Cell 2016.
48. Miner JJ, Cao B, Govero J, Smith AM, Fernandez E, Cabrera OH, Garber C, Noll M, Klein RS, Noguchi KK, Mysorekar IU, Diamond MS. Zika Virus Infection during Pregnancy in Mice Causes Placental Damage and Fetal Demise. Cell 2016;165:1081-1091. http://dx.doi.org/10.1016/j.cell.2016.05.008 PMid:27180225
49. Tappe D, Perez-Giron JV, Zammarchi L, Rissland J, Ferreira DF, Jaenisch T, Gomez-Medina S, Gunther S, Bartoloni A, Munoz-Fontela C, Schmidt-Chanasit J. Cytokine kinetics of Zika virus-infected patients from acute to reconvalescent phase. Med Microbiol Immunol 2016;205:269-273. http://dx.doi.org/10.1007/s00430-015-0445-7 PMid:26702627 PMCid:PMC4867002
50. Dejnirattisai W, Supasa P, Wongwiwat W, Rouvinski A, Barba-Spaeth G, Duangchinda T, Sakuntabhai A, Cao-Lormeau VM, Malasit P, Rey FA, Mongkolsapaya J, Screaton GR. Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. Nat Immunol 2016;17:1102-1108. http://dx.doi.org/10.1038/ni.3515 PMid:27339099
51. Cao-Lormeau VM, Blake A, Mons S, Lastere S, Roche C, Vanhomwegen J, Dub T, Baudouin L, Teissier A, Larre P, Vial AL, Decam C, Choumet V, Halstead SK, Willison HJ, Musset L, Manuguerra JC, Despres P, Fournier E, Mallet HP, Musso D, Fontanet A, Neil J, Ghawche F. Guillain-Barre Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet 2016;387:1531-1539. http://dx.doi.org/10.1016/S0140-6736(16)00562-6
52. World Health Organization. Situation Report. Zika virus, Microcephaly and Guillain-Barré syndrome. 1 June 2016. 2016.
53. World Health Organization. Guillain-Barré syndrome – Brazil. Disease Outbreak News. 8 February 2016. World Health Organization website: http://www.who.int/csr/don/8-february-2016-gbs-brazil/en/. consulted on June 12, 2016 2016.
54. Kleber de Oliveira W, Cortez-Escalante J, De Oliveira WT, do Carmo GM, Henriques CM, Coelho GE, Araujo de Franca GV. 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 2016;65:242-247. http://dx.doi.org/10.15585/mmwr.mm6509e2 PMid:26963593
55. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound Obstet Gynecol 2016;47:6-7.
56. CDC. Recognizing, managing, and reporting Zika virus infections in travelers returning from Central America, South America, the Caribbean, and Mexico. CDC Health Advisory. Atlanta, GA: US Department of Health and Human Services, CDC 2016.
57. European Centre for Disease Prevention and Control. Rapid risk assessment: microcephaly in Brazil potentially linked to the Zika virus epidemic. 2015.
58. WHO. Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome. 2016.
59. Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, Pessoa A, Doriqui MJ, Neri JI, Neto JM, Wanderley HY, Cernach M, El-Husny AS, Pone MV, Serao CL, Sanseverino MT. Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65:59-62. http://dx.doi.org/10.15585/mmwr.mm6503e2 PMid:26820244
60. Victora CG, Schuler-Faccini L, Matijasevich A, Ribeiro E, Pessoa A, Barros FC. Microcephaly in Brazil: how to interpret reported numbers? Lancet 2016;387:621-624.
61. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, Salje H, Van Kerkhove MD, Abadie V, Garel C, Fontanet A, Mallet HP. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. Lancet 2016;387:2125-2132. http://dx.doi.org/10.1016/S0140-6736(16)00651-6
62. Johansson MA, Mier YT-RL, Reefhuis J, Gilboa SM, Hills SL. Zika and the Risk of Microcephaly. N Engl J Med 2016.
63. Brasil P, Pereira JP, Jr., Raja Gabaglia C, Damasceno L, Wakimoto M, Ribeiro Nogueira RM, Carvalho de Sequeira P, Machado Siqueira A, Abreu de Carvalho LM, Cotrim da Cunha D, Calvet GA, Neves ES, Moreira ME, Rodrigues Baiao AE, Nassar de Carvalho PR, Janzen C, Valderramos SG, Cherry JD, Bispo de Filippis AM, Nielsen-Saines K. Zika Virus Infection in Pregnant Women in Rio de Janeiro - Preliminary Report. N Engl J Med 2016.
64. Hazin AN, Poretti A, Turchi Martelli CM, Huisman TA, Di Cavalcanti Souza Cruz D, Tenorio M, van der Linden A, Pena LJ, Brito C, Gil LH, de Barros Miranda-Filho D, Marques ET, Alves JG. Computed Tomographic Findings in Microcephaly Associated with Zika Virus. N Engl J Med 2016;374:2193-2195. http://dx.doi.org/10.1056/NEJMc1603617 PMid:27050112
65. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, Sacramento GA, Ko AI, Maia M, Belfort R, Jr. Ocular Findings in Infants With Microcephaly Associated With Presumed Zika Virus Congenital Infection in Salvador, Brazil. JAMA Ophthalmol 2016.
66. Carteaux G, Maquart M, Bedet A, Contou D, Brugieres P, Fourati S, Cleret de Langavant L, de Broucker T, Brun-Buisson C, Leparc-Goffart I, Mekontso Dessap A. Zika Virus Associated with Meningoencephalitis. N Engl J Med 2016;374:1595-1596. http://dx.doi.org/10.1056/NEJMc1602964 PMid:26958738
67. Mecharles S, Herrmann C, Poullain P, Tran TH, Deschamps N, Mathon G, Landais A, Breurec S, Lannuzel A. Acute myelitis due to Zika virus infection. Lancet 2016;387:1481. http://dx.doi.org/10.1016/S0140-6736(16)00644-9
68. Roze B, Najioullah F, Signate A, Apetse K, Brouste Y, Gourgoudou S, Fagour L, Abel S, Hochedez P, Cesaire R, Cabie A. Zika virus detection in cerebrospinal fluid from two patients with encephalopathy, Martinique, February 2016. Euro Surveill 2016;21.
69. Arzuza-Ortega L, Polo A, Perez-Tatis G, Lopez-Garcia H, Parra E, Pardo-Herrera LC, Rico-Turca AM, Villamil-Gomez W, Rodriguez-Morales AJ. Fatal Sickle Cell Disease and Zika Virus Infection in Girl from Colombia. Emerg Infect Dis 2016;22:925-927. http://dx.doi.org/10.3201/eid2205.151934 PMid:27089120 PMCid:PMC4861530
70. Pan American Health Organization, World Health Organization. Epidemiological alert. Neurological syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas. 2015 2015.
71. Magurano F, Zammarchi L, Baggieri M, Fortuna C, Farese A, Benedetti E, Fiorentini C, Rezza G, Nicoletti L, Bartoloni A. Chikungunya from the Caribbean: the importance of appropriate laboratory tests to confirm the diagnosis. Vector Borne Zoonotic Dis 2015;15:258-260. http://dx.doi.org/10.1089/vbz.2014.1724 PMid:25897812
72. Zammarchi L, Stella G, Mantella A, Bartolozzi D, Tappe D, Gunther S, Oestereich L, Cadar D, Munoz-Fontela C, Bartoloni A, Schmidt-Chanasit J. Zika virus infections imported to Italy: clinical, immunological and virological findings, and public health implications. J Clin Virol 2015;63:32-35. http://dx.doi.org/10.1016/j.jcv.2014.12.005 PMid:25600600
73. Venturi G, Zammarchi L, Fortuna C, Remoli ME, Benedetti E, Fiorentini C, Trotta M, Rizzo C, Mantella A, Rezza G, Bartoloni A. Authors' reply: diagnostic challenges to be considered regarding Zika virus in the context of the presence of the vector Aedes albopictus in Europe. Euro Surveill 2016;21.
74. Johnson BW, Kosoy O, Martin DA, Noga AJ, Russell BJ, Johnson AA, Petersen LR. West Nile virus infection and serologic response among persons previously vaccinated against yellow fever and Japanese encephalitis viruses. Vector Borne Zoonotic Dis 2005;5:137-145. http://dx.doi.org/10.1089/vbz.2005.5.137 PMid:16011430
75. Huzly D, Hanselmann I, Schmidt-Chanasit J, Panning M. High specificity of a novel Zika virus ELISA in European patients after exposure to different flaviviruses. Euro Surveill 2016;21.

76. European Centre for Disease Prevention and Control. Interim guidance for healthcare providers and Zika virus laboratory diagnosis. ECDC TECHNICAL DOCUMENT 2016.
77. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. Emerg Infect Dis 2015;21:84-86. http://dx.doi.org/10.3201/eid2101.140894 PMid:25530324 PMCid:PMC4285245
78. 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;21.
79. Driggers RW, Ho CY, Korhonen EM, Kuivanen S, Jaaskelainen AJ, Smura T, Rosenberg A, Hill DA, DeBiasi RL, Vezina G, Timofeev J, Rodriguez FJ, Levanov L, Razak J, Iyengar P, Hennenfent A, Kennedy R, Lanciotti R, du Plessis A, Vapalahti O. Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities. N Engl J Med 2016;374:2142-2151. http://dx.doi.org/10.1056/NEJMoa1601824 PMid:27028667
80. Baud D, Van Mieghem T, Musso D, Truttmann AC, Panchaud A, Vouga M. Clinical management of pregnant women exposed to Zika virus. Lancet Infect Dis 2016.
81. Centers for Disease Control and Prevention. Guidelines for Travelers Visiting Friends and Family in Areas with Chikungunya, Dengue, or Zika. CDC Web site. Consulted on August 7, 2016. Available at: http://wwwnc.cdc.gov/travel/page/guidelines-vfr-chikungunya-dengue-zika 2016.
82. Wylie BJ, Hauptman M, Woolf AD, Goldman RH. Insect Repellants During Pregnancy in the Era of the Zika Virus. Obstet Gynecol 2016.
83. Oduyebo T, Igbinosa I, Petersen EE, Polen KN, Pillai SK, Ailes EC, Villanueva JM, Newsome K, Fischer M, Gupta PM, Powers AM, Lampe M, Hills S, Arnold KE, Rose LE, Shapiro-Mendoza CK, Beard CB, Munoz JL, Rao CY, Meaney-Delman D, Jamieson DJ, Honein MA. Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure - United States, July 2016. MMWR Morb Mortal Wkly Rep 2016;65:739-744. http://dx.doi.org/10.15585/mmwr.mm6529e1 PMid:27467820
84. Bocanegra C, Sulleiro E, Soriano-Arandes A, Pou D, Suy A, Llurba E, Rodo C, Espasa M, Campins M, Martin A, Rodrigo C, Vazquez A, De Ory F, Sanchez-Seco MP, Pumarola T, Carreras E, Molina I. Zika virus infection in pregnant women in Barcelona, Spain. Clin Microbiol Infect 2016.
85. Ministero della Salute. Piano Nazionale di sorveglianza e risposta alle arbovirosi trasmesse da zanzare (Aedes sp.) con particolare riferimento a virus Chikungunya, Dengue e virus Zika - 2016. Circolare 0017200-16/06/2016-DGPRE-DGPRE-P. Available at: http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf;jsessionid=TR1zmYYqgDn9E34D+9A4yg__.sgc3-prd-sal?anno=2016&codLeg=55229&parte=1%20&serie=null. Consulted on August 8, 2016 2016.
86. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika Virus. N Engl J Med 2016;374:1552-1563. http://dx.doi.org/10.1056/NEJMra1602113 PMid:27028561
87. Fleming-Dutra KE, Nelson JM, Fischer M, Staples JE, Karwowski MP, Mead P, Villanueva J, Renquist CM, Minta AA, Jamieson DJ, Honein MA, Moore CA, Rasmussen SA. Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection--United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65:182-187. http://dx.doi.org/10.15585/mmwr.mm6507e1 PMid:26914500
88. Larocca RA, Abbink P, Peron JP, Zanotto PM, Iampietro MJ, Badamchi-Zadeh A, Boyd M, Ng'ang'a D, Kirilova M, Nityanandam R, Mercado NB, Li Z, Moseley ET, Bricault CA, Borducchi EN, Giglio PB, Jetton D, Neubauer G, Nkolola JP, Maxfield LF, Barrera RA, Jarman RG, Eckels KH, Michael NL, Thomas SJ, Barouch DH. Vaccine protection against Zika virus from Brazil. Nature 2016.
89. Martins KA, Dye JM, Bavari S. Considerations for the development of Zika virus vaccines. Vaccine 2016;34:3711-3712. http://dx.doi.org/10.1016/j.vaccine.2016.06.012 PMid:27318417
90. Medlock JM, Hansford KM, Versteirt V, Cull B, Kampen H, Fontenille D, Hendrickx G, Zeller H, Van Bortel W, Schaffner F. An entomological review of invasive mosquitoes in Europe. Bull Entomol Res 2015;105:637-663. http://dx.doi.org/10.1017/S0007485315000103 PMid:25804287
91. Gjenero-Margan I, Aleraj B, Krajcar D, Lesnikar V, Klobucar A, Pem-Novosel I, Kurecic-Filipovic S, Komparak S, Martic R, Duricic S, Betica-Radic L, Okmadzic J, Vilibic-Cavlek T, Babic-Erceg A, Turkovic B, Avsic-Zupanc T, Radic I, Ljubic M, Sarac K, Benic N, Mlinaric-Galinovic G. Autochthonous dengue fever in Croatia, August-September 2010. Euro Surveill 2011;16.
92. Succo T, Leparc-Goffart I, Ferre JB, Roiz D, Broche B, Maquart M, Noel H, Catelinois O, Entezam F, Caire D, Jourdain F, Esteve-Moussion I, Cochet A, Paupy C, Rousseau C, Paty MC, Golliot F. Autochthonous dengue outbreak in Nimes, South of France, July to September 2015. Euro Surveill 2016;21.
93. Marchand E, Prat C, Jeannin C, Lafont E, Bergmann T, Flusin O, Rizzi J, Roux N, Busso V, Deniau J, Noel H, Vaillant V, Leparc-Goffart I, Six C, Paty MC. Autochthonous case of dengue in France, October 2013. Euro Surveill 2013;18:20661. http://dx.doi.org/10.2807/1560-7917.ES2013.18.50.20661 PMid:24342514
94. La Ruche G, Souares Y, Armengaud A, Peloux-Petiot F, Delaunay P, Despres P, Lenglet A, Jourdain F, Leparc-Goffart I, Charlet F, Ollier L, Mantey K, Mollet T, Fournier JP, Torrents R, Leitmeyer K, Hilairet P, Zeller H, Van Bortel W, Dejour-Salamanca D, Grandadam M, Gastellu-Etchegorry M. First two autochthonous dengue virus infections in metropolitan France, September 2010. Euro Surveill 2010;15:19676.
95. Rezza G, Nicoletti L, Angelini R, Romi R, Finarelli AC, Panning M, Cordioli P, Fortuna C, Boros S, Magurano F, Silvi G, Angelini P, Dottori M, Ciufolini MG, Majori GC, Cassone A. Infection with chikungunya virus in Italy: an outbreak in a temperate region. Lancet 2007;370:1840-1846. http://dx.doi.org/10.1016/S0140-6736(07)61779-6
96. Delisle E, Rousseau C, Broche B, Leparc-Goffart I, L'Ambert G, Cochet A, Prat C, Foulongne V, Ferre JB, Catelinois O, Flusin O, Tchernonog E, Moussion IE, Wiegandt A, Septfons A, Mendy A, Moyano MB, Laporte L, Maurel J, Jourdain F, Reynes J, Paty MC, Golliot F. Chikungunya outbreak in Montpellier, France, September to October 2014. Euro Surveill 2015;20.
97. Outbreak news. Chikungunya, Spain. Wkly Epidemiol Rec 2015;90:409.
98. European Centre for Disease Prevention and Control. Zika virus disease epidemic: Preparedness planning guide for diseases transmitted by Aedes aegypti and Aedes albopictus. ECDC 2016.
99. Petersen EE, Polen KN, Meaney-Delman D, Ellington SR, Oduyebo T, Cohn A, Oster AM, Russell K, Kawwass JF, Karwowski MP, Powers AM, Bertolli J, Brooks JT, Kissin D, Villanueva J, Munoz-Jordan J, Kuehnert M, Olson CK, Honein MA, Rivera M, Jamieson DJ, Rasmussen SA. 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. http://dx.doi.org/10.15585/mmwr.mm6512e2 PMid:27031943
100. World Health Organization. Prevention of sexual transmission of Zika virus Interim guidance update 7 June 2016. WHO/ZIKV/MOC/16.1 Rev.2 2016.
101. European Centre for Disease Prevention and Control. Zika virus and safety of substances of human origin - A guide for preparedness activities in Europe. . ECDC 2016.