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ABBREVIATIONS

CCHFV	*Crimean-Congo hemorrhagic fever virus*
CHIKV	*Chikungunya virus*
CHPV	*Chandipura virus*
CI	Confidence interval
CSF	Cerebrospinal fluid
CTFV	*Colorado tick fever virus*
CVV	*Cache Valley virus*
DENV	*Dengue virus*
EEEV	*Eastern equine encephalitis virus*
JEV	*Japanese encephalitis virus*
KFDV	*Kyasanur Forest disease virus*
LACV	*La Crosse virus*
LIV	*Looping ill virus*
MAYV	*Mayaro virus*
MTCT	Mother to child transmission
OR	Odds ratio
ONNV	*O'Nyong nyong virus*
OROV	*Oropouche virus*
RRV	*Ross River virus*
RT-PCR	Reverse-transcriptase polymerase chain reaction
RVFV	*Rift Valley fever virus*
SFTSV	*Severe fever and thrombocytopenia syndrome virus*
SINV	*Sindbis virus*
SLEV	*Saint Louis encephalitis virus*
TBEV	*Tick-borne encephalitis virus*
TOSV	*Toscana virus*
VEEV	*Venezuelan equine encephalitis virus*
WEEV	*Western equine encephalitis virus*
WG	Weeks of gestation
WNV	*West Nile virus*
YFV	*Yellow fever virus*
ZIKV	*Zika virus*

ABSTRACT
Arboviruses are an expanding public health threat, with pregnant women facing unique complications. Arbovirus infections can be more severe in pregnant women than in the general population, for e.g. dengue and Crimean-Congo hemorrhagic fever. Vertical transmission is reported for many arboviruses and can severely affect pregnancy outcome. Indeed, arboviruses are associated with increased risks of fetal losses and prematurity, in particular Flaviviruses and Alphaviruses. Arboviruses can be teratogenic, as for *Zika virus* and *Venezuelan equine encephalitis virus*. Intrapartum transmission can finally result in severe neonatal infections, as for Chikungunya virus. Although the global burden of arboviruses is well recognized, little data focus specifically on mother-child health and arbovirus infection. Epidemiological and clinical studies are therefore needed to better assess the burden of arbovirus infections during pregnancy and improve their prevention and clinical management. Here we review available information and point out gaps of knowledge requiring further assessment.

INTRODUCTION
Arboviruses are viruses transmitted by arthropod vectors. More than 100 arbovirus species are pathogenic to humans. They belong to six main RNA virus families (*Togaviridae*, *Flaviviridae*, *Bunyaviridae*, as well as *Reoviridae*, *Rhabdoviridae* and *Orthomyxoviridae),* and therefore exhibit a high level of genetic variability. Arbovirus infections typically manifest as fever, possibly associated with cutaneous, joint, neurological and/or hemorrhagic symptoms and signs.
The recent emergence of *Zika virus* and the identification of its teratogenicity illustrate the threat posed by arboviruses to pregnant women and their fetus, and many other arboviruses are associated with maternal-fetal pathologies.[1] All inhabited continents face emerging, re-emerging or highly endemic arbovirus infections, as illustrated by the recent outbreaks of *Zika virus*, of *Chikungunya virus* which has spread from Africa to the Indian Ocean, Asia and the Americas, or of *West Nile virus* (which spread throughout North America over the last decade; by the increasing burden of *Dengue virus* (10^8 cases / year globally); and by the recent reemergence of *Yellow fever virus* infections (2 x 10^5 cases / year globally).[2-4] Of the estimated 210,000,000 annual pregnancies worldwide, 90% occur in areas where arboviruses are endemic or epidemic, while the remaining 10% pregnant women may be exposed sporadically, considering the increasing number of pregnant travelers.[5,6]
As an illustration of arbovirus threat to pregnant women, it is estimated that around 10% of pregnant women were infected by *Chikungunya virus* during the 2005-2006 outbreak in La Réunion, and 2·8% of Brazilian pregnant women had serological evidence of recent *Dengue virus* infection in the 2008-2009 outbreak.[7,8] As of April 2017, around 17,000 pregnant women have been infected by *Zika virus* in Brazil alone.[9] Considering that arbovirus infections are under-diagnosed and underreported in endemic areas, the actual number of infected pregnant women is likely far larger.
The threat of arbovirus infections during pregnancy may expose to three distinct risks: (*i*) more severe infection in pregnant women than in the general adult population, (*ii*) mother-to-child transmission (MTCT) before delivery (*antepartum*) with deleterious consequences on pregnancy and fetus, including teratogenic effects, and (*iii*) MTCT during delivery (*intrapartum*) resulting in severe neonatal infection. The severity of these potential complications contrasts with the current lack of available detailed clinical data, preventive and curative strategies.[10,11] Here we review the available epidemiological, virological, clinical and therapeutic data on major arbovirus infections in pregnancy and identify gaps of knowledge that need to be addressed on this important biomedical topic.

EPIDEMIOLOGY AND VECTORS
The classification and epidemiological features of the main arboviruses responsible for human diseases are listed in table 1, 2 and 3.
Human arboviruses transmission involves three factors: (*i*) a vertebrate reservoir, (*ii*) blood-sucking arthropods that act as biological vectors, and (*iii*) the human host that can be infected as spillover events and become secondary reservoir in urban settings, such as for *Dengue virus, Chikungunya virus* and *Zika virus*.[3,4] The array of vectors involved is usually narrow for a given arbovirus species, but involves altogether a wide variety of species of mosquitoes, ticks, midges, and sandflies.
Arboviruses are widely distributed (figure 1 A-C), reflecting multiple factors that include the type, competence and distribution of their respective vector(s); geographic and climate variables; presence of enzootic cycles acting as amplifying reservoirs.[56] As a result, the geographic distribution of arbovirus species is uneven and constantly evolving. Some arboviruses are, at least so far, restricted to specific regions: *Japanese encephalitis virus* is present in Asia where *Yellow fever virus* is absent [57], *Dengue virus* circulates in all tropical/subtropical areas and *Tick-borne encephalitis virus* only in Central and Eastern Europe, and Asia.[58,59] Other arbovirus species have (re)-emerged as local outbreaks, and then spread on a large scale, like *West Nile virus* which emerged on the East of the USA in 1999, and then spread to the West coast in the next 5 years; *Chikungunya*

virus which spread from East Africa to the Indian Ocean and Asia (2004-2007) and emerged in the Americas in 2014; or *Zika virus*, originating from Africa, which emerged in the Pacific Islands in 2008 and reached South and Central Americas in 2015 from where it has since amplified massively.[3,4] Imported travel-related cases have also resulted in clusters of autochthonous arbovirus transmission in temperate areas where their vector is implanted, like *Chikungunya virus* in Italy in 2007.[60] Other arboviruses remain geographically very limited, like *Kyasanur Forest disease virus* in Karnataka state in India, *Oropouche virus*, *Mayaro virus* or *Cache Valley virus* in America, but these viruses might spread if conditions promoting transmission arise.[61] For example, in Egypt, the Aswan dam construction was responsible for major vector amplification that led to *Rift Valley fever virus* - related abortion storms in cattle and subsequent spread of this epizootic to humans.[62] Climate changes have also been proposed as a possible trigger of *Bunyaviridae* spreading around the Mediterranean basin, and in particular of *Crimean-Congo hemorrhagic fever virus* in Madrid, Spain in August 2016.[63,64] These unanticipated cases illustrate the possibility of arbovirus emergence outside of the tropics if the right conditions are met. The factors responsible for the current global arbovirus outburst have been extensively studied.[3] They combine anthropogenic factors (increased human transportation, deforestation, urbanization, rainwater storage, poor sanitation conditions), inefficient vector control/resistance to insecticides, and climate change including El Niño and global warming).[56] These conditions favor contacts between permissive hosts and competent vectors and also facilitate vector amplification and extension beyond tropical latitudes. Selection of virus variants, through emergence of isolates with enhanced virulence and/or enhanced vector or vertebrate host fitness have also been proposed.[3]

MATERNAL CLINICAL PRESENTATION

As in the non-pregnant host, arbovirus infections typical clinical presentation in pregnant women varies according to the virus involved but they share common features. Incubation is short, typically less than a week after arthropod bite. Three main patterns are observed, which may overlap:

- Fever and flu-like symptoms with or without rash (e.g. *Zika virus, Dengue virus*, *Chikungunya virus*, *Oropouche virus, and West Nile virus*)
- Encephalitis/meningoencephalitis (e.g. *Japanese encephalitis virus*, *Tick-borne encephalitis virus*, *Saint Louis encephalitis virus*, *Venezuelan equine encephalitis virus*, *Western and Eastern equine encephalitis viruse*s, *La Crosse virus*, *Ross River virus*, *West Nile virus*, *Toscana virus*, *Colorado tick fever virus* and *Chandipura virus*, and less commonly *Dengue virus*, *Chikungunya virus* and *Zika virus)*
- Hemorrhagic fever (e.g. *Yellow fever virus*, *Rift Valley fever virus*, *Crimean-Congo hemorrhagic fever virus* and *Dengue virus*).

Yet, in most cases and for most arboviruses, infection is asymptomatic, with the notable exceptions of *Chikungunya virus* [2] (symptomatic in above 85%), of *Yellow fever virus* [65] and Asian lineage of *Zika virus* (symptomatic in 50%). [66] Mortality varies according to the causative agent and clinical presentation. It is reported in up to 30% in hemorrhagic fever and/or shock syndrome complicating *Crimean-Congo hemorrhagic fever virus*, *Japanese encephalitis virus*, *Yellow fever virus*, *Tick-borne encephalitis virus*, and *Dengue virus* infections, but anecdotally reported in others. Most infections resolve without sequelae, except those caused by neurotropic viruses that can result in long-term neurological defects. For instance, *Japanese encephalitis virus*, which mostly affects children, is responsible for persisting neurological disabilities in more than 30% of surviving patients.[59] Also, less severe complications such as long-lasting articular disease or persisting fatigue after viral clearance can be reported with arthrogenic alphaviruses (mainly *Chikungunya virus*, *Mayaro virus*, and *Ross River virus*) and *Dengue virus*, respectively.

Until recently, pregnancy was not identified in epidemiological studies as a specific risk factor for severe arbovirus infection, in contrast to other infections like influenza, varicella, measles and malaria that are notably more severe during pregnancy. Hemorrhagic symptoms are a threat to pregnant women, and the two notable exceptions to this rule are *Dengue virus* and *Crimean-Congo hemorrhagic fever virus*, both arboviruses associated with hemorrhagic complications.[67,68] Indeed, arbovirus hemorrhagic complications not only increase maternal mortality, but also expose infected mothers to higher rates of C-section and post-partum hemorrhages with additional life-threatening consequences.[50,69] Indeed, a significant increase in severe dengue (dengue hemorrhagic fever and/or shock syndrome) has been reported in pregnant women in Brazil, especially during the second and third pregnancy trimesters, as compared to non-pregnant women of reproductive age (odds ratio [OR] 3·38; Confidence interval [CI] 2·10-5·42).[11] The mortality rate reached 22% in pregnant Sudanese women diagnosed with dengue hemorrhagic fever and/or shock (mortality of non-pregnant women of reproductive age was not reported in this study).[70] Maternal mortality rate reached 34% in pregnant women with Crimean-Congo hemorrhagic fever, which is likely higher than in the general population.[48,49]

FETAL AND NEONATAL CONSEQUENCES OF MATERNAL INFECTION

When maternal arbovirus infection is reported, obstetrical follow-up should include evaluation of placental function, of fetal vitality and growth, with careful ultrasound detection and characterization of fetus developmental defects and of clinical and radiological neonatal abnormalities. Few arboviruses have been studied in detail with regard to their direct and indirect impact on the fetal-placental unit, and almost all available data are derived from the arboviruses of the *Togaviridae* and *Flaviridae* families. The spectrum of fetal and/or neonatal complications encompasses:

- Fetal losses (miscarriages < 28 weeks of gestation (WG) and stillbirths thereafter)[9] (mostly for *Dengue virus*, *Japanese encephalitis virus, Zika virus,* and *Venezuelan equine encephalitis virus*), premature delivery and low birthweight for gestational age (mostly *Dengue virus*)
- Developmental defects/teratogenicity (*Zika virus* and *Venezuelan equine encephalitis virus*)
- Perinatal infection (defined as neonatal infection occurring either upon *intrapartum* contamination, or after late *antepartum* contamination, within the last days of pregnancy) (*Chikungunya virus*, to a lower extent *Dengue virus* and as case reports *Yellow fever virus, Zika virus, and Western equine encephalitis virus*)[12,21,22,27,29,30,38,42,47,69,71]
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Dengue virus: *Dengue virus* is associated with a significant risk of adverse fetal outcome. In a recent meta-analysis, Paixao *et al*. evidenced that overt dengue is associated with an increased risk of miscarriage (OR 3·51, 95% CI 1·15–10·77), of stillbirth (crude relative risk 6·7, 95% CI 2·1–21·3), preterm birth (OR 1·71, 95% CI 1·06–2·76), and low birthweight for gestational age (OR 1·41, 95% CI 0·90–2·21).[27,29] Fetal losses are reported until 25 WG.[27] Fetal losses correlate with maternal symptoms' severity, and fetal loss rates in mothers with asymptomatic infection does not differ from the pregnant uninfected population.[29] Brazilian data suggest that maternal sickle cell disease, a genetic trait highly prevalent in Latin America and Africa, might increase dengue-associated risk of fetal loss.[72] Whether serotype has an impact on fetal loss remains unknown. Perinatal *Dengue virus* transmission is also reported in case of maternal symptoms occurring 10 days around delivery, yet its actual incidence is unknown.[30,73] Of note, maternal *Dengue virus*-specific antibodies passively transmitted to the fetus confer protection for neonates towards dengue at first, but also increases the risk of severe infection in dengue involving another *Dengue virus* serotype. This phenomenon, referred to as antibody-dependent enhancement, results from antibody-mediated facilitation of virus infection of FCR-bearing cells.[74,75]

Japanese encephalitis virus: Japanese encephalitis virus is responsible for miscarriages that are only reported when maternal infection occurs until 22 WG (4/4 aborted fetuses with evidence of *Japanese encephalitis virus* infection until 22 WG versus 0/4 cases after 22 WG in the only available case series).[32,76]

West Nile virus: A single observation reported a congenitally acquired *West Nile virus*-associated encephalitis and chorioretinitis after maternal infection at 27 WG, but subsequent large epidemiological studies showed no increased risk for fetal infection or demise, nor any long-term neurological impairment in children borne from mothers infected during their pregnancy.[35,77,78]

Venezuelan equine encephalitis virus: Venez*uelan equine encephalitis virus* is associated with frequent miscarriages, stillbirths and premature deliveries, as observed during the large 1962 and 1995 Venezuelan outbreaks. Autopsies could be performed in 10 cases and Venez*uelan equine encephalitis virus* was evidenced in the brain of aborted fetuses.[2,20] Single observations of infants born to mothers who experienced Venezuelan equine encephalitis between 13 to 36 WG also evidenced neurological disorders that led to classify Venez*uelan equine encephalitis virus* as the first teratogenic arbovirus.[79] These infants presented with fatal cerebral lesions ranging from extensive necrosis to hydranencephaly, with neuronal and astrocytes abnormalities.[79] Of note, Venez*uelan equine encephalitis virus* is an alphavirus, which belong to *Togaviridae* family that also includes *Rubella virus*, a notorious teratogenic virus associated with a severe congenital syndrome.

Zika virus: Asian lineage *Zika virus* has recently emerged, and medical observations as well as experimental investigations have led to the conclusion that *Zika virus* is a major teratogenic arbovirus, and the only one so far of the *Flaviviridae* family in human. *Zika virus* was until 2015 considered as causing only a benign illness in rural areas of Africa, where it is endemic, before it emerged in Micronesia (5,000 people affected), French Polynesia (100,000) and massively spread to Latin America, where *Zika virus* high incidence in a non-immune population living in a highly-medicalized area led to the identification of its association with fetal complications.[39,80] Data collected in Brazil, and retrospective analysis of data from French Polynesia demonstrated the temporal and geographical association between *Zika virus* infection in pregnant women and fetal losses, growth restriction or fetal and neonatal developmental defects, initially identified as "microcephaly".[39,81] Altogether, the "congenital Zika syndrome" now includes microcephaly, which can be associated to other brain abnormalities that include eye lesions (including malformations, optic neuritis, chorioretinal scarring and atrophy), hearing loss, cranio-facial and musculoskeletal lesions likely resulting from fetal akinesia deformation sequence (arthrogryposis, lung hypoplasia, flat midface, scoliosis, and limb deformations).[82,83] Autopsy data have evidenced cerebral ventriculomegaly, lyssencephaly, cerebellar hypoplasia and agyria.[84-87] Microscopic brain lesions include micro-calcifications, gliosis, neuronal and glial cells

degeneration and necrosis located at the subcortical-cortical transition, and also perivascular infiltrate of T and B cells in the subcortical white matter and Wallerian degeneration of the long descending tracts.[87] Reduced placental function with fetal growth restriction and fetal loss is also reported when maternal infection occurs up to 32WG.[42] The rate of brain abnormalities at birth in infants born from *Zika virus* -infected mothers is estimated from 1% to 13%[39,40], with a recent 5.9% estimation in an cohort from the USA.[43] The peak of fetal susceptibility to *Zika virus* congenital syndrome appears to be the first trimester of pregnancy, although 14% of infants with *Zika virus* -associated microcephaly in the Brazilian cohort had maternal infection in the second trimester; brain calcification and hemorrhages have also been evidenced in 2 fetuses infected at 34 and 39WG, respectively.[42] Long-term postnatal neurological consequences of *Zika virus* fetal infection remain to be fully determined. A preliminary study on 48 Brazilian infants report poor cranial growth, irritability, pyramidal/extrapyramidal symptoms, and epilepsy at up to 8 months of age, including in children without microcephaly at birth. [46]

Chikungunya virus: Chikungunya virus is responsible for neonatal infection that occurs as a consequence of *intrapartum* contamination and is now recognized from large epidemiological studies as a major complication of maternal chikungunya.[8] Vertical transmission occurs in up to half of mothers who are viremic during labor.[12] Neonatal symptoms develop between 3-7 days of life, and range from mild presentation (43%) to severe infection with encephalitis (53%) requiring transfer in intensive care unit.[8] Fever and acute respiratory distress are also reported.[12] This presentation is hardly distinguishable from bacterial sepsis, and diagnosis is challenging when maternal infection has not been diagnosed. Neonatal Chikungunya neurological disease can have a dramatic impact on postnatal neurological development: recent data evidence a significantly lower median Development Quotient (86 versus 100, $p<0.001$) at the age of 2 years and a significant proportion of moderate to severe global neurodevelopmental delays (51% versus 15%, $p<0.001$) in infants with perinatal infection when compared to uninfected matched controls.[88]

Ross river virus: In contrast to *Chikungunya virus* -associated severe fetal outcomes, *Ross river virus* MTCT has been reported as asymptomatic, and associated with no neonatal pathology.[17]

PATHOPHYSIOLOGY

Mechanisms associated with increased maternal severity in dengue and Crimean-Congo hemorrhagic fever are unknown, although the impact of utero-placental hemorrhages might be involved, especially in low-resources countries where access to transfusion and surgery is limited. Fetal and neonatal complications may result from four complementary processes: (*i*) acute fetal distress in the context of a severe maternal infection impairing maternal hemodynamics, and therefore placental/fetal oxygenation, (*ii*) placental arbovirus infection with subsequent reduction of the blood flow to the fetus without fetal infection, (*iii*) fetal and neonatal infection in the context of virus crossing of the placental barrier, and (*iv*) neonatal infection in the context of labor-associated placental breaches (figure 2).[89]

Maternal hemodynamic changes might have an impact on placental perfusion and thereby on the developing fetus. This has been recently suggested for dengue. Indeed, histopathological analyses of placenta collected at delivery from *Dengue virus* -infected mothers have evidenced hypoxic lesions with villous stroma edema, infarcted and pre-infarcted areas in 19/24 cases, including 8 from mothers who did not report overt shock syndrome.[72] This is also the most likely scenario accounting for fetal losses in severe Crimean-Congo hemorrhagic fever, although not proven.

Placental arbovirus infection can induce placental dysfunction, with subsequent adverse fetal outcome. It is one of the most likely causes of the fetal losses, premature deliveries and low birthweights reported in dengue. Indeed, the same histopathological studies also evidenced chorio-deciduitis and villitis; immunostaining evidenced viral antigens in the decidual cells trophoblasts and villous stroma cells in 22/24 cases that overlapped with histological lesions in 10.[72]

Placental arbovirus infection can also lead to *antepartum* MTCT, which can either be asymptomatic, lead to fetal death, and/or to developmental defects (teratogenicity). MTCT associated with fetal death has been poorly studied in human, and is only documented for *Zika virus* and *Japanese encephalitis virus*, but largely reported in other mammals for many arboviruses, like *Venezuelan equine encephalitis virus* in mice and mares, *Western equine encephalitis virus* in rhesus macaques, *Ross river virus* in mice, *Japanese encephalitis virus* in swine and *West Nile virus* in mice or *Rift valley fever virus* in ruminants.[8,90-93] The events and timing associated with fetal/litter losses are far from being fully elucidated. It is assumed that the sooner the maternal infection occurs, the most severe the fetal consequences are, as evidenced in mice for *West Nile virus* and *Japanese encephalitis virus*, and in *Japanese encephalitis virus* in humans as reported above.[93,94]

Veterinary medicine observations of developmental defects in the offspring after epizootic events has provided the first basis incriminating arboviruses as teratogenic, long before the ongoing *Zika virus* outbreak. Developmental defects include brain lesions, whatever the arbovirus family involved, in line with the observation that most other vertically transmitted-pathogens are also neurotropic, like *Rubella virus*, bacteria such as *Listeria monocytogenes, Treponema pallidum*, and protozoans such as *Toxoplasma gondii.* A teratogenic

effect has been reported for *Rift valley fever virus* and *Cache valley virus* in calves, *Saint Louis encephalitis virus* in mice and with other animal arboviruses that have never been described in humans so far, like *Wesselsbron virus* (calves), *Bovine viral diarrhea virus* (calves) or *Banzi virus* (sheeps) (all *Flaviviridae*), *Schmallenberg virus* (calves) or *Akabane virus* (goats and calves) (both *Bunyaviridae*) or *Blue tongue virus* (calves) (*Reoviridae*).[95-98] In humans, only *Venezuelan equine encephalitis virus* and *Zika virus* have been proven teratogenic. *Venezuelan equine encephalitis virus* was first incriminated in 1977, but detailed pathophysiological data are not available. Experiments performed in rats evidenced the presence of viral antigens on the cyto- and syncytiotrophoblasts.[99] *Venezuelan equine encephalitis virus* was confirmed teratogenic in a Rhesus monkey model of infection (microcephaly, hydrocephaly), however the mechanisms of viral crossing of the placental barrier and teratogenicity have not been elucidated.[100] In contrast, *Zika virus* pathogenicity has been extensively studied since 2015, in context of its massive dissemination in Latin America. Clinical, experimental and epidemiological studies have demonstrated the teratogenicity of *Zika virus*, based on temporality, biological plausibility, strength of association, exclusion of alternative explanations, cessation, animal experiments, consistency and analogy with other teratogenic pathogens (reviewed in [80]). *Zika virus* exhibits unique properties responsible for the *Zika virus* congenital syndrome: it is able to cross the placental barrier, multiply in the placenta and disseminate to the fetus, targeting the cortical progenitors of the brain, thereby inducing microcephaly. Data from *in vitro* cultured cells and placenta explants show that *Zika virus* is able to infect the extra villous cytotrophoblast but not the mature syncytiotrophoblast.[101,102] How *Zika virus* reaches these extra villous cytotrophoblastic cells that are not directly accessible from the maternal bloodremains to be elucidated. In the placenta, *Zika virus* can multiply in resident macrophages, called Hofbauer cells, as evidenced from histological data, explant and cultured cells experiments.[101,103] They might amplify *Zika virus* infection, along with infected placental endothelial cells, and favor its release in the fetal circulation.[82] In the fetus, *Zika virus* is neurotropic, with high viral RNA titers found in the brain, as compared to the lungs, spleen and liver.[87,104,105] The mechanisms associated with *Zika virus* access to the fetal brain remain to be uncovered. In the fetal brain parenchyma *Zika virus* seems to be the unique flavivirus able to infect cortical progenitors. It has also been recently evidenced in vitro that DENV-antibodies cross-react with *Zika virus* and thereby enhance Zika infection; this could have important clinical consequences as both viruses are highly prevalent in Latin America, and also for the development of vaccines against both viruses.[106]

Intrapartum contamination without actual placental infection is a direct consequence of maternal viremia and fetal/neonatal susceptibility to a given arbovirus species. It has been well documented for *Chikungunya virus*, which, in contrast to *Zika virus*, is not able to infect the placenta.[8,10] It is therefore not transmitted to the fetus in the absence of placental breaches, that allow a transfer of maternal blood to the fetal/neonatal circulation. Indeed, *Chikungunya virus* cannot be detected as replicating in the placenta from viremic mothers, and human syncytiototrophoblastic cell lines are refractory to infection *in vitro*.[10] This was confirmed by experimental infections performed in a model of gestant IFN-α/βR$^{-/-}$ mice, where placentas constitute an absolute barrier to *Chikungunya virus* that protect highly susceptible fetuses from CHIKV infection despite high maternal viremia.[10]

DIAGNOSIS OF ARBOVIRUS INFECTIONS

Diagnostic procedures in pregnant women do not differ from those used in the general population. Biological abnormalities, that include lymphopenia, thrombocytopenia and increased serum transaminase levels, can mimic a pregnancy-associated complication called HELLP syndrome (that can precede eclampsia and is characterized by Hemolysis, Elevated liver enzymes, Low Platelet count), and therefore delay diagnosis. Virological diagnosis relies on arbovirus-specific reverse-transcriptase polymerase chain reaction (RT-PCR) assays in blood or cerebrospinal fluid (CSF), and on serological assays (IgM detection, IgG seroconversion and/or 4-fold increase in IgG titers on sera collected at 10-14 days' interval). RT-PCR in the blood is limited to the diagnosis of the arboviruses responsible for high viremia during the first days of symptoms, like *West Nile virus, Dengue virus, Chikungunya virus* and *Zika virus*.[65] Detection of virus-specific IgM in the CSF can also be performed.[107] *Zika virus* RNA is also detectable in the urine for 14 to 21 days.[108]

The diagnosis of fetal infection would be based on RT-PCR on amniotic fluid or fetal blood to prove MTCT. The added value of antenatal screening for arboviruses has not been precisely evaluated (and the procedure may actually favor MTCT), apart from *Zika virus* given its notable teratogenic effect, for which amniocentesis is considered on an individual basis, when pregnancy termination would be medically considered, and ethically and legally authorized.[109] Clinicians should be aware that biological samples with suspected or demonstrated level-3 (most arboviruses in non-endemic areas) and level-4 pathogens (like *Crimean Congo hemorrhagic fever virus*) require adequate management in authorized facilities.

PREVENTION OF MATERNAL INFECTION

Vector control and limitation of contact with arthropods is key for arbovirus infection prevention. General protective measures for pregnant women are similar to those for the general population, such as covering the

exposed skin, checking for tick-bites (for *Crimean Congo hemorrhagic fever virus*), using window and door screens, bed nets, and if possible air-conditioning. The use of insects repellent at recommended dosage is considered safe for pregnant women.[110,111]

Commercial vaccines are available against *Japanese encephalitis virus, Tick-borne encephalitis virus, and Yellow fever virus*. There is no available data regarding the use of inactivated *Japanese encephalitis virus* and *Tick-borne encephalitis virus* vaccines during pregnancy. They do not expose the fetus to infectious risk, but given the lack of large cohort studies, they should only be administered after careful individual risk-benefit assessment.[112] Most experts would recommend their use in pregnant women in case of high exposure to mosquito bite in areas of autochthonous arbovirus transmission. Live-attenuated *Japanese encephalitis virus* vaccines are not recommended during pregnancy. Even though the live-attenuated *Yellow fever virus* vaccine is classically contraindicated during pregnancy, the World Health Organization recommends its administration in pregnancy if travel to endemic area is unavoidable.[113] This recommendation results from the apparent safety of yellow fever vaccine in pregnant women in large scale vaccination campaigns in Africa and Brazil, and from the severity of the disease and persisting burden in unvaccinated population.[114,115] The first life-attenuated dengue vaccine was recently registered.[116] The lack of data in pregnant women and usual restrictions about live vaccines in pregnancy precludes for now its use in this setting. A formalin-inactivated vaccine for *Rift valley fever virus* and an inactivated vaccine against *Kyasanur Forest disease virus* are also developed but not widely available; and there is no data on their use during pregnancy.[117] To date, there is still no commercially-available vaccine against *Chikungunya virus*. Passive immunization with polyclonal immunoglobulins is effective in preventing *Crimean Congo hemorrhagic fever virus*, *Rift valley fever virus* and *West Nile virus* infections, but has not been studied in pregnancy.[118-120] Regarding *Zika virus*, although there is a consensus that a vaccine able to prevent *Zika virus* -associated fetopathy is critically warranted, testing the efficacy and safety of such a vaccine in pregnant women is poised to be challenging, as risks associated with *Zika virus* to be prevented by vaccination should outweigh risks associated with the prescription of a new biological preparation in the pregnant host.

MATERNAL ANTIVIRAL TREATMENT

No specific anti-arbovirus drug is commercially available. Ribavirin has been considered useful in some extremely severe arbovirus diseases like *Crimean Congo hemorrhagic fever virus* and *Rift valley fever virus*, but its demonstrated teratogenic effect precludes its use during pregnancy, except in life-threatening maternal infections.[121] BCX4430, an adenosine nucleoside analog with broad-spectrum antiviral properties against RNA viruses, is currently investigated. It has demonstrated *in vitro* activity towards *Filoviridae, Bunyaviridae*, and *Flaviviridae*, including mosquito-borne species (*Yellow fever virus*, *Japanese encephalitis virus*, *Dengue virus 2, West Nile virus*, African and Asian lineages of *Zika virus*) and tick-borne species (*Tick-borne encephalitis virus*, *Kyasanur Forest disease virus*, *Looping ill virus*).[122] It has been reported as active *in vitro* and *in vivo* in a mouse model of Zika, and recently entered phase I human clinical studies in healthy volunteers with promising pharmacokinetics and tolerance.[123,124]

Drug repurposing also suggest a potential antiviral effect for ivermectin and azithromycin. Ivermectin is an anti-helminthic drug with antiviral properties that inhibits flaviviruses' replication by targeting the NS3 helicase activity.[125] A clinical trial is currently evaluating its efficacy in Thailand (NCT02045069). If proven beneficial, this would open new interesting opportunities for the treatment of maternal dengue, considering the safety of ivermectin during pregnancy.[126] Azithromycin is a macrolide that is considered safe in pregnancy. It has recently been shown to exhibit an antiviral effect on *Zika virus*.[127]

Whole genome RNAi and CRISPR/Cas9 screens have helped identify multiple druggable host pathways for which antiviral development is currently under way.[128,129]

NEONATAL THERAPEUTIC STRATEGIES

Passive immunotherapy by infusion of immunoglobulins can prevent MTCT, as reported for Hepatitis B. They can reduce viral load and therefore the burden of neonatal infection.[130] Such strategies could be extremely promising in the field of arbovirus infections.

Polyvalent immunoglobulins purified from plasma obtained from chikungunya-convalescent human donors have been shown protective and curative in a mouse model of chikungunya.[131] Anti-*chikungunya virus* hyper-immune immunoglobulins are under evaluation to assess their safety and efficacy in the prevention of *chikungunya virus* MTCT in neonates born to viremic mothers (CHIKIVIG-01, clinical trials NCT02230163). Similar approaches have been reported against *West Nile virus* but not evaluated in pregnancy.[132]

GAPS IN KNOWLEDGE

Key messages from this review are (*i*) the severity of maternal Dengue and Crimean-Congo hemorrhagic fever, (*ii*) the risk of fetal losses associated with flaviviruses (*Dengue virus* and *Japanese encephalitis virus*), (*iii*) the teratogenicity of *Zika virus* and *Venezuelan equine encephalitis virus*, and (*iv*) the severity of *intrapartum* arbovirus MTCT, in particular for *Chikungunya virus*. However, there remain many unknowns regarding the

actual burden of arbovirus infections during pregnancy.

The true incidence of arbovirus infections in pregnancy has not been precisely assessed, nor the true incidence of adverse fetal outcome.[133] This lack of knowledge results from a combination of parameters: (*i*) epidemiological factors (co-existence of different arboviruses in the same geographic areas, current rarity of some arbovirus infections) (*ii*) medical factors, as most arbovirus infections can be asymptomatic; (*iii*) socio-economic factors, considering the worldwide heterogeneity of health care access for pregnant women and neonates, of diagnostic procedures availability, of care seeking behavior for self-limited infections or fetal loss, and finally (*iv*) methodological factors, as many studies lack the statistical power to detect obstetrical consequences in contexts of low/unknown arbovirus incidence.[19,134,135] Dedicated prospective studies, based on large population data are urgently needed, along with the systematic report of sporadic cases, including imported cases in high-resource countries. Sustainable and interconnected surveillance systems are mandatory to better assess epidemiological signals. Current evidence argues for a more systematic and exhaustive laboratory work-up in cases of fetal loss or fever with compatible syndromes in pregnant women, and for a systematic assessment of long-term developmental consequences in congenital arbovirus infections.

Pathophysiological mechanisms responsible for arbovirus-associated increased maternal severity, fetal losses, developmental defects and neonatal pathology remain understudied. *Zika virus* is a remarkable illustration of how the detailed study of a virus and the pathologies it induces can progress dramatically within a 1-year window. Similar studies are now critically needed for other highly prevalent arboviruses which are here to stay, and for which a precise characterization of their impact on pregnancy is lacking.

Finally, therapeutic trials dedicated to mother and child issues are also urgently needed: infectious diseases remain the first cause of maternal death worldwide.[136] Improving our understanding of arbovirus infections in pregnancy and their medical management might turn out to help reach two of the eight millennium developmental goals set by the United Nations and the Bill and Melinda Gates Foundation: improve maternal health and reduce child mortality.[137]

SEARCH STRATEGY AND SELECTION CRITERIA

We searched in PubMed, Embase, Web of science (Thomson Reuters) and Cochrane Central databases for all reports published up to March 31, 2017 using the terms “arbovirus”, “pregnancy”, “newborn”, “fetal” and “placenta”. A second search was performed replacing the generic term “arbovirus” with the name of each individual known arbovirus, such as “Chikungunya”, Venezuelan equine” Japanese encephalitis”, Dengue” and so on. The complete list of terms and search strategy are available in supplementary material. Language restrictions were: English, French, Spanish and German.

KEY MESSAGES

- Dengue and Crimean-Congo hemorrhagic fever infections are more severe in pregnancy
- Flaviviruses and especially *Dengue virus* and *Japanese encephalitis virus* are associated with increased risk of fetal losses
- *Zika virus* and *Venezuelan equine encephalitis virus* are teratogenic
- *Intrapartum* arbovirus Mother-to-child transmission may cause severe neonatal disease, in particular for *Chikungunya virus*
- The actual burden of arbovirus infections during pregnancy remain uncovered.

Legends

Figure 1. World distribution of major arbovirus infections.

Figure 2. Patterns of pathophysiological events associated with adverse fetal/ neonatal outcome.

Table 1. Classification, epidemiological features, maternal risk and consequences of mother to child transmission of major *Togaviridae* in humans.

WG: Weeks of gestation

USA: United States

Miscarriages refer to fetal losses < 28 WG

Stillbirths refer to fetal losses ≥ 28 WG

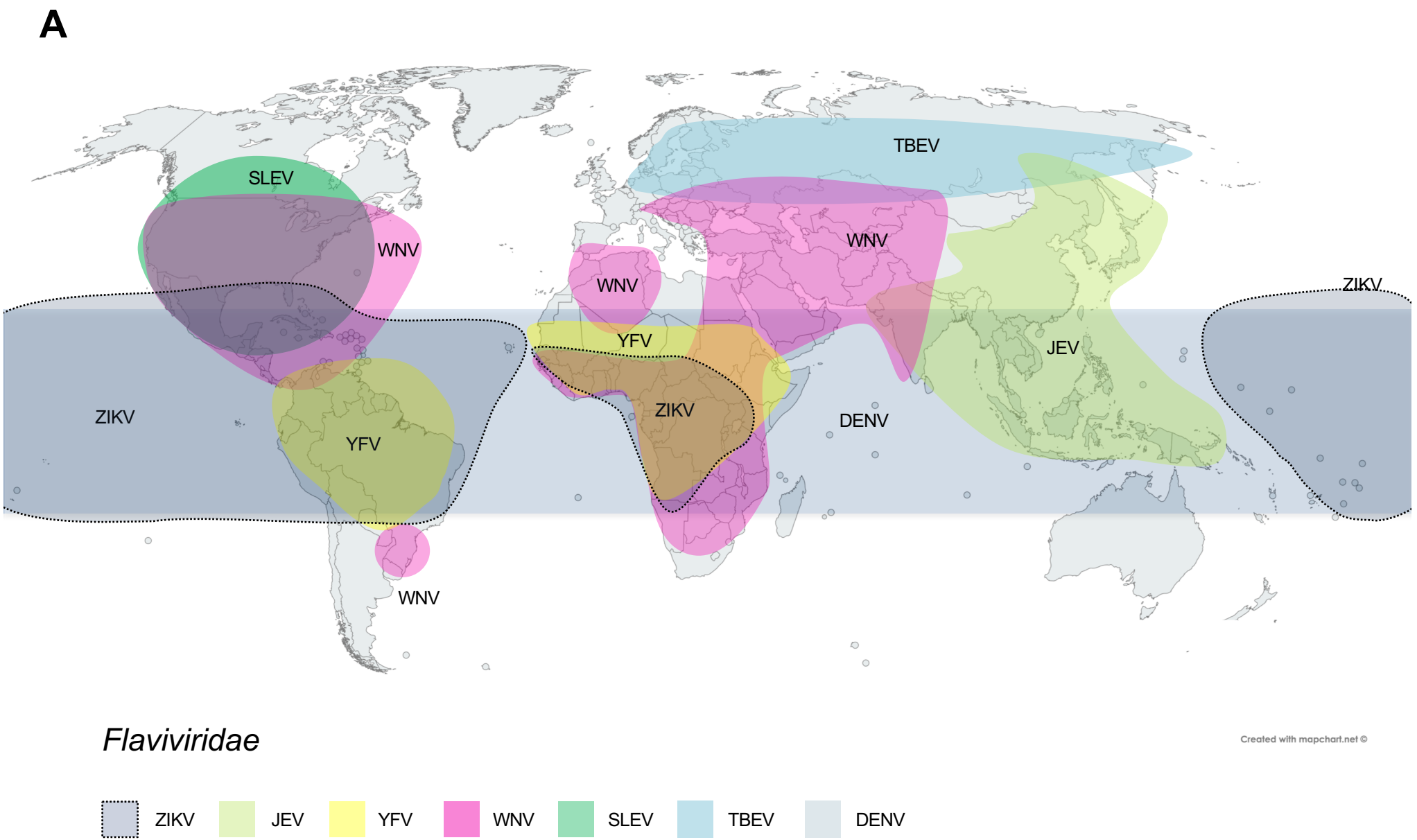
Table 2. Classification, epidemiological features, maternal risk and consequences of mother to child transmission of major *Flaviviridae* in humans.
WG: Weeks of gestation
USA: United States
Miscarriages refer to fetal losses < 28 WG
Stillbirths refer to fetal losses ≥ 28 WG

Table 3. Classification, epidemiological features, maternal risk and consequences of mother to child transmission of major *Bunyaviridae*, *Reoviridae* and *Rhabdoviridae* in humans
WG: Weeks of gestation
USA: United States
Miscarriages refer to fetal losses < 28 WG
Stillbirths refer to fetal losses ≥ 28 WG

Contributors
CC and ML conceived the review. CC, TC and MCB reviewed the literature. CC and ML wrote the manuscript. All authors approved the manuscript.

The authors declared no conflicts of interest

Figure 1


A
TBEV
SLEV
WNV
WNV
WNV
ZIKV
YFV
JEV
ZIKV
ZIKV
DENV
YFV
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Flaviviridae
Created with mapchart.net ©
ZIKV
JEV
YFV
WNV
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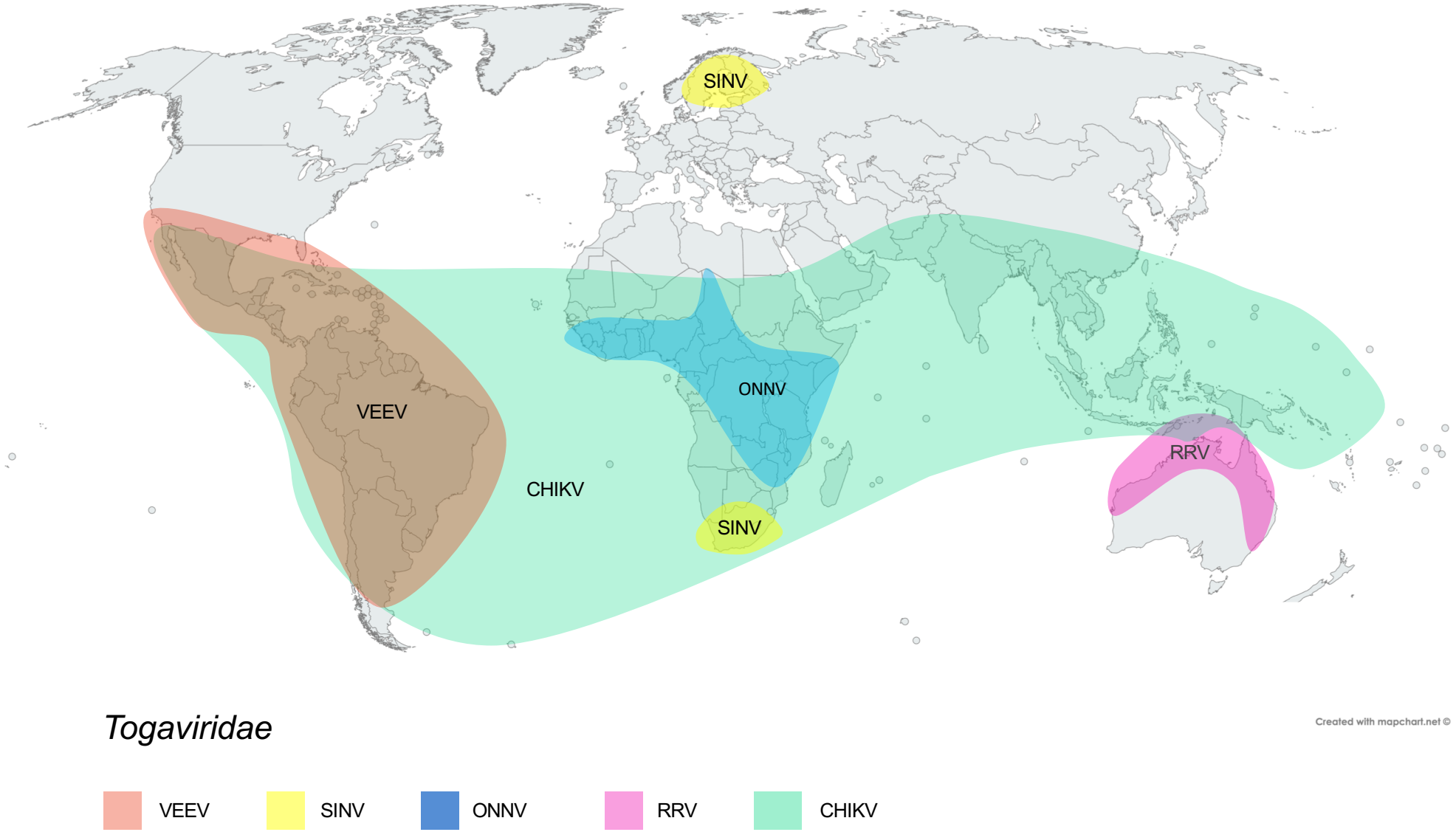
TBEV
DENV

B



Togaviridae

VEEV SINV ONNV RRV CHIKV

C

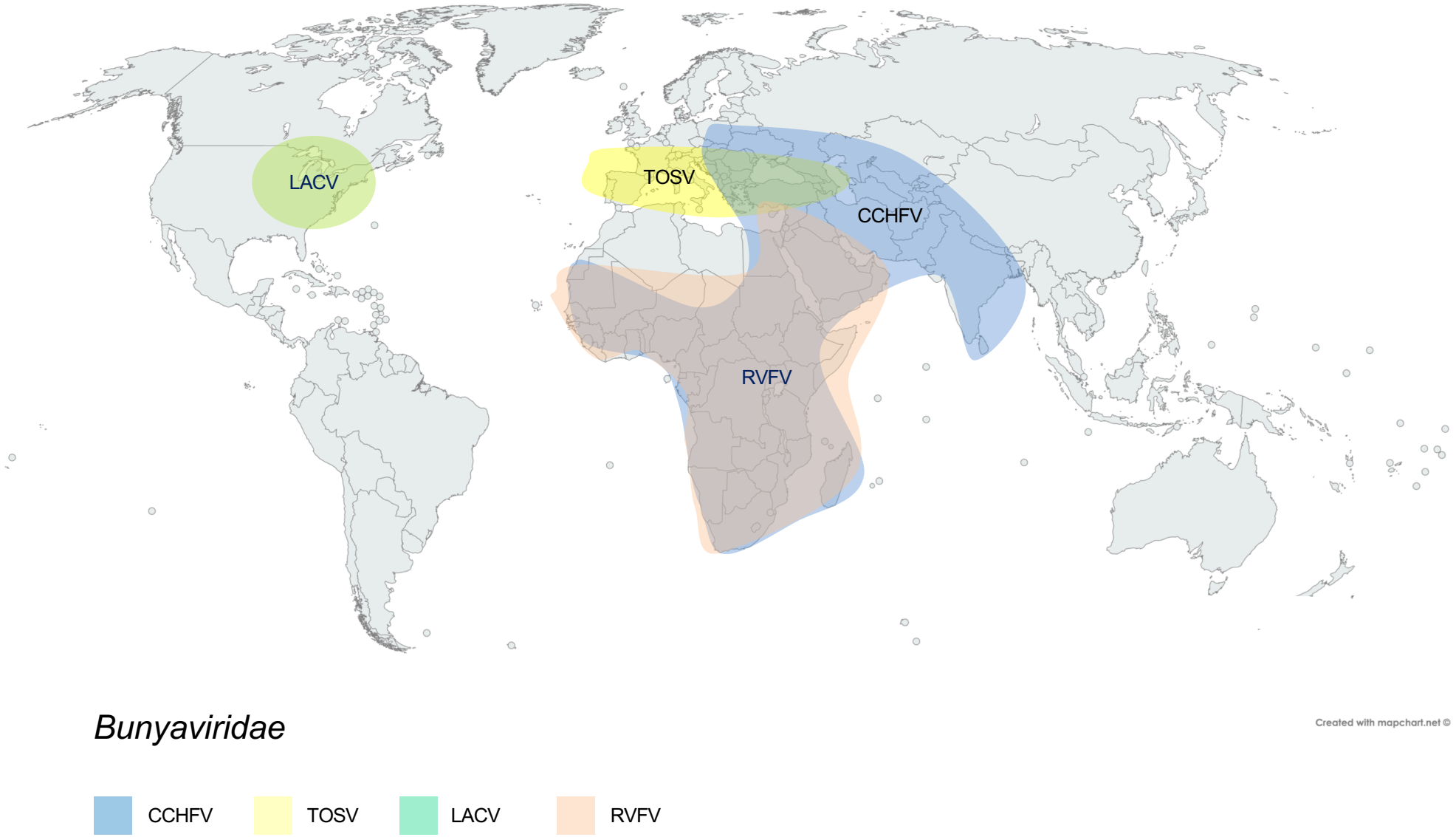

LACV
TOSV
CCHFV
RVFV
Bunyaviridae
Created with mapchart.net ©
CCHFV
TOSV
LACV
RVFV

Figure 2

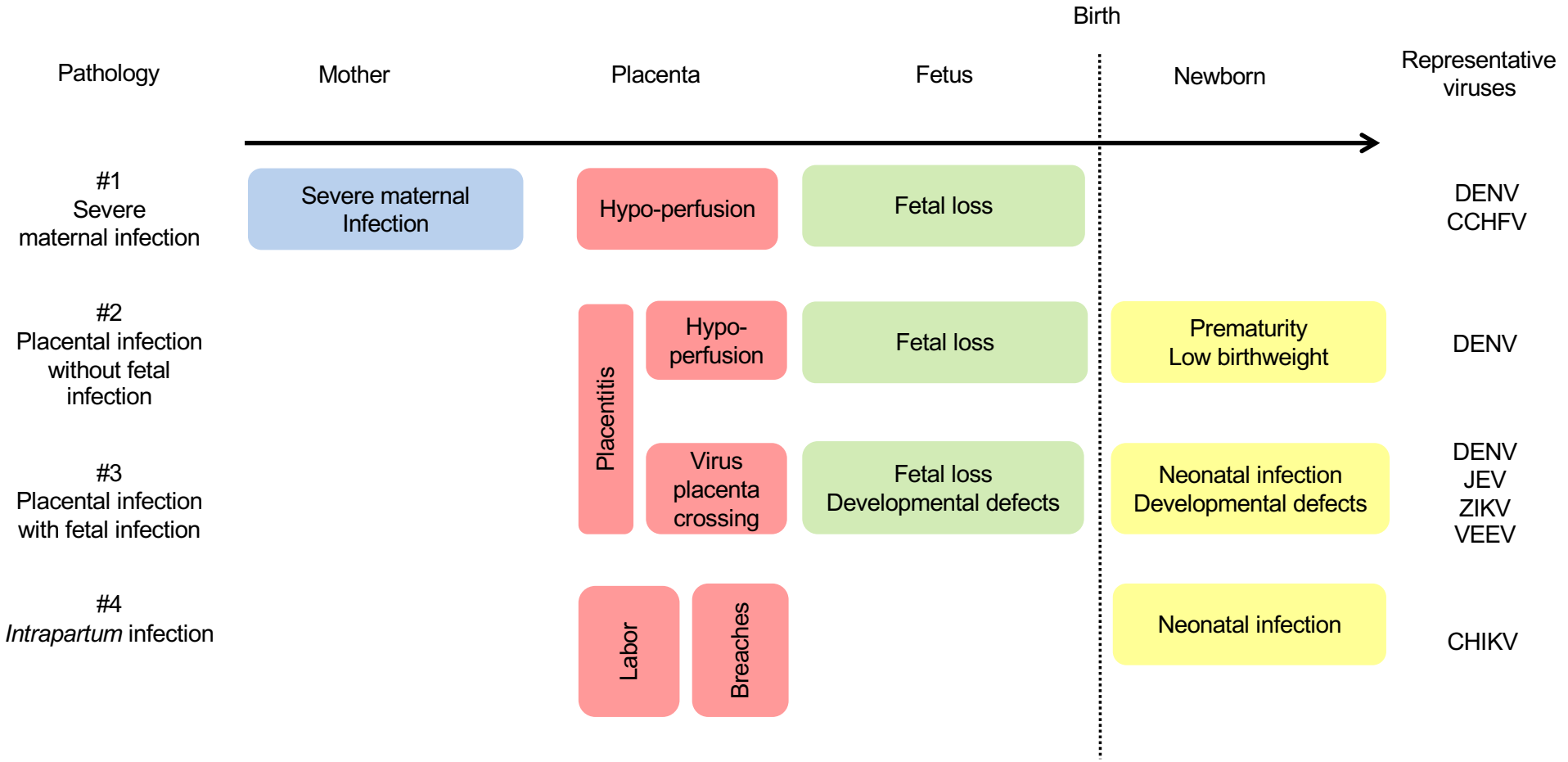

Birth
Pathology
Mother
Placenta
Fetus
Newborn
Representative viruses
#1 Severe maternal infection
Severe maternal Infection
Hypo-perfusion
Fetal loss
DENV
CCHFV
#2 Placental infection without fetal infection
Placentitis
Hypo-perfusion
Fetal loss
Prematurity
Low birthweight
DENV
#3 Placental infection with fetal infection
Virus placenta crossing
Fetal loss
Developmental defects
Neonatal infection
Developmental defects
DENV
JEV
ZIKV
VEEV
#4 Intrapartum infection
Labor
Breaches
Neonatal infection
CHIKV

Table 1.

Family / virus	Area	Main vectors	Maternal risk	Antenatal consequences of mother to child transmission	Perinatal consequences of mother to child transmission
Barmah forest disease virus (BFDV)	Australia	Mosquito (*Culex sp.)*	No data	No data	No data
Chikungunya virus (CHIKV)	America (tropical areas) Africa Asia Australia Indian Ocean	Mosquito (*Aedes sp.)*	No increased risk of severe maternal infection	Transmission documented Low incidence - Miscarriages documented in 2% in one study (3/678) (No increase of stillbirths, prematurity or malformation [8])	Documented Incidence: transmission rate of 28-49% with severe neonatal infection in 53% of newborn (encephalopathy) in one study [8,12] - Severe neonatal infection with encephalopathy in 4 studies [8,13-15]
Eastern equine encephalitis virus (EEEV)	America (North, Central and South)	Mosquito (*Culiseta* sp.*)*	No data	No data	No data
Mayaro virus (MAYV)	South America	Mosquito (*Aedes* sp.)	No data	No data	No data
O'Nyong-nyong virus (ONNV)	Central Africa	Mosquito (*Anopheles* sp.)	No data	Transmission uncertain - 2 miscarriages reported, but link to infection unknown (fetuses untested) [16]	No data
Ross river virus (RRV)	Australia Pacific area	Mosquito (*Aedes sp.* and *Culex* sp.*)*	No data	Transmission documented - 3% asymptomatic transmission in one single series [17]	No data
Sindbis virus (SINV)	Africa Asia Australia Europe (Fennoscandia)	Mosquito (*Aedes* sp., *Culex* sp., *and Culiseta* sp.*)*	No data	Transmission uncertain - 2 stillbirths reported, including one following overt maternal infection at 32 WG (fetuses untested) [18]	No data
Venezuelan equine encephalitis virus (VEEV)	America (Central and South)	Mosquito (*Culex* sp.*)*	No data	Transmission documented Incidence unknown (data from 2 small case-series) - VEEV documented in the brain of 10 aborted fetuses [19] - Developmental brain lesions in infants born from mothers infected 13-36 WG [20]	No data
Western equine encephalitis virus (WEEV)	America (North, Central and South)	Mosquito (*Aedes* sp. and *Culex* sp.*)*	No data	No data	Documented Incidence unknown - 3 cases with severe encephalitis, including one fatal [21,22]

Table 2.

Family / virus	Area	Main vectors	Maternal risk	Antenatal consequences of mother to child transmission	Perinatal consequences of mother to child transmission
Dengue virus (DENV)	Worldwide (Tropical areas)	Mosquito (*Aedes* sp.)	Documented risk of severe infection: hemorrhagic and/or shock syndrome Odds ratio 3·38 from a recent meta-analysis [11, 23-26]	Transmission documented - Increased rate of fetal losses in the first half of pregnancy (data from multiple cohorts, confirmed in a meta-analysis) [27-29]	Documented Incidence unknown - Severe neonatal infection with sepsis-like symptoms and acute respiratory distress reported as case-reports [30, 31]
Japanese encephalitis virus (JEV)	Asia Australia	Mosquito (*Culex* sp.)	No data	Transmission documented and severe Incidence unknown - Fetal losses documented only in maternal infections occurring < 22 WG (1 Indian series of 8 cases) [32]	No data
Kyasanur forest disease / Alkhurma virus (KFDV)	Asia (Middle East, India South-East and Western Asia)	Tick (*Haemophysalis* sp.)	No data	No data	No data
Murray Valley encephalitis virus (MVEV)	Australia Papua New Guinea	Mosquito (*Culex* sp.)	No data	No data	No data
Powassan virus	North America	Tick (*Ixodes* sp.)	No data	No data	No data
Saint Louis encephalitis virus (SLEV)	America (North and Central)	Mosquito (*Culex* sp.)	No data	No data	No data
Tick-borne encephalitis virus (TBEV)	Northern Europe and North Asia (in a belt extending from eastern Europe to Japan)	Tick (*Ixodes* sp.)	No data	No data	No data
West Nile virus (WNV) (also known as Kunjin virus in Oceania)	Worldwide Most prevalent in America and Africa Low prevalence in Europe	Mosquito (*Culex* sp.)	No data	Transmission documented Exceptional - One case of congenital chorioretinitis and encephalitis after maternal infection at 27 WG [33] - No significant increase in fetal losses/adverse long term neurological outcome in US cohort studies [34-36]	Uncertain - 2 cases with encephalitis developing 6-10 days after birth (maternal symptoms 21-6 days before delivery, no documentation of viral infection at birth) [35] - 1 case with transient rash at birth and positive IgM 1 month later (maternal symptoms at birth) [35]
Yellow fever virus (YFV)	Sub-Saharan Africa South America	Mosquito (*Aedes* sp. or *Haemagogus* sp.)	No data	Transmission documented Exceptional - 2 cases of fatal maternal infection at 4 and 5 months of pregnancy with lesions compatible with YFV in the fetuses [37]	Documented Probably exceptional - One single fatal report (maternal symptoms onset 3 days before delivery) [38]
Zika virus (ZIKV)	South Pacific area Latin America Caribbean USA (Florida & Puerto Rico)	Mosquito (*Aedes* sp.)		Transmission documented Incidence : 1-13% brain abnormalities at birth[39, 40] -Demonstrated teratogenic according to multiple case-reports and case series [41] - Severe microcephaly and other brain lesions [39, 42, 43] - Retinal lesions [44] - Prematurity or fetal losses [45] - Organogenesis and weight usually preserved [45] - Impaired postnatal neurological development with poor cranial growth, irritability, pyramidal/extrapyramidal symptoms, and epilepsy.[46]	Documented Probably exceptional - 2 French Polynesian case reports of possible perinatal transmission (one asymptomatic, one with mild rash)[47]

Table 3.

Family / virus	Area	Main vectors	Maternal risk	Antenatal consequences of mother to child transmission	Perinatal consequences of mother to child transmission
Crimean-Congo hemorrhagic fever virus (CCHFV)	Europe (South-East and Eastern) Africa Middle East Asian countries south of the 50th parallel	Midge (*Culicoides* sp.) Tick (> 30 species involved)	Documented increased risk of severe infection: Increased mortality rate (34% in a recent review of 42 available case reports and short case series) [48]	Transmission documented Incidence unknown - 4 miscarriages at 4-19 WG (fetuses untested) (reviewed in [48]) - Stillbirths with maternal death (data from two case series) [48, 49]	Documented Incidence unknown - One case with documented fatal neonatal infection [50]
La Crosse virus (LACV)	North America (Mid-western and eastern)	Mosquito (*Aedes* sp.)	No data	Transmission documented Incidence unknown - One asymptomatic mother-to child transmission documented serologically in cord serum, after a maternal infection at 21 WG [51]	No data
Oropouche virus (OROV)	America (Central and South)	Midge (*Culicoides* sp.)	No data	No data	No data
Rift Valley fever virus (RVFV)	Africa Middle East Asia	Mosquito (*Aedes sp., Culex sp. and Anopheles* sp.)	No data	Transmission documented -Increased risk of miscarriages in a recent cross-sectional study comparing miscarriages in pregnant patients with documented RVFV (15/28, 54%) versus 12/103 (12%) in pregnant women with documented CHIKV infection [52]	Documented Incidence unknown - 2 symptomatic cases. Infants borne from mothers symptomatic 4-6 days before delivery. Symptoms were present at birth or 4 days after delivery (one with rash and organomegaly, and one with disseminated fatal infection). [53, 54]
Severe fever with thrombocytopenia syndrome virus (SFTSV)	Asia (Eastern China Japan and Corea)	Not completely elucidated Evidenced in Ticks *Haemaphisalis* sp.)	No data	No data	No data
Tahyna virus (TAHV)	Europe Africa Asia	Mosquito (*Culex* sp.)	No data	No data	No data
Toscana virus (TOSCV)	Europe	Sand-fly (*Phlebotomus* sp.)	No data	No data	No data
Colorado tick fever virus (CTFV)	North America	Tick (*Dermacentor* sp.)	No data	Transmission uncertain - 2 miscarriages after maternal infections (fetuses not tested)[55]	Uncertain One possible case (fever and leucopenia in a neonate delivered 6 days after maternal infection onset) [55]
Chandipura virus (CHPV)	Asia	Sand-fly (*Sergentomyia* sp.)	No data	No data	No data

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