Arboviruses and pregnancy: maternal, fetal, and neonatal effects

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Arboviruses are an expanding public health threat, with pregnant women facing unique complications from arbovirus infections. These infections, such as dengue and Crimean–Congo haemorrhagic fever, can be more severe in pregnant women than in the general population. Vertical transmission is reported for many arboviruses and can severely affect pregnancy outcome. Indeed, arboviruses—particularly flaviviruses and alphaviruses—are associated with increased risks of fetal loss and premature birth. Arboviruses can be teratogenic, as is the case for Zika virus and Venezuelan equine encephalitis virus. Finally, intrapartum transmission can result in severe neonatal infections, as is true for chikungunya virus. Although the global burden of arboviruses is well recognised, few studies have provided data on arbovirus infection specifically in the context of maternal and child health. Epidemiological and clinical studies are therefore needed to better assess the burden of arbovirus infections during pregnancy and to improve the prevention and clinical management of these viral infections. In this Review, we analyse the information available and identify gaps in knowledge that require further assessment.

Introduction

Arboviruses are viruses transmitted by arthropod vectors. More than 100 arbovirus species are pathogenic to human beings. They belong to six main RNA virus families (Togaviridae, Flaviviridae, Bunyaviridae, Reoviridae, Rhabdoviridae, and Orthomyxoviridae), and therefore exhibit high genetic variability. Arbovirus infections typically manifest as fever, possibly associated with cutaneous, joint, neurological, or haemorrhagic symptoms and signs.

The 2015–16 outbreak of Zika virus and the identification of its teratogenicity illustrate the threat posed by arboviruses to pregnant women and their fetuses; many other arboviruses are associated with maternal and fetal pathologies.[1] All inhabited continents face emerging, re-emerging, or highly endemic arbovirus infections, as highlighted by the recent outbreaks of Zika virus, chikungunya virus (which has spread from Africa to the Indian Ocean, Asia, and the Americas), and West Nile virus (which has spread throughout North America in the past decade); by the increasing burden of dengue virus (1×10^8 cases each year globally); and by the recent re-emergence of yellow fever virus infections (2×10^5 cases each year globally).[2–4] Of the estimated $2{\cdot}1\times10^8$ annual pregnancies worldwide, 90% occur in areas where arboviruses are endemic or epidemic, while the remaining 10% of pregnant women could be exposed to these viruses sporadically, in view of the increasing number of pregnant travellers.[5,6] Approximately 10% of pregnant women were estimated to have been infected by chikungunya virus during the 2005–06 outbreak in La Réunion, Brazil, and 2·8% of Brazilian pregnant women had serological evidence of dengue virus infection in the 2008–09 outbreak.[7,8] As of April, 2017, approximately 17 000 pregnant women have been infected by Zika virus in Brazil alone.[9] Considering that arbovirus infections are under-diagnosed and under-reported in endemic areas, the actual number of infected pregnant women is probably far higher.

Arbovirus infections during pregnancy could expose pregnant women to three distinct risks: more severe infection in pregnant women than in the general adult population; mother-to-child transmission before delivery (ie, antepartum transmission), with deleterious consequences on pregnancy and the fetus, including teratogenic effects; and mother-to-child transmission during delivery (intrapartum), resulting in severe neonatal infection. The severity of these potential complications contrasts with the scarcity of available detailed clinical data, and of preventive and curative strategies.[10,11] In this Review, we discuss the available epidemiological, virological, clinical, and therapeutic data on major arbovirus infections in pregnancy and identify gaps in knowledge that need to be addressed (appendix).

Key messages

- Arboviruses are an expanding public health threat; some arbovirus infections, such as dengue and Crimean–Congo haemorrhagic fever, are more severe in pregnant women than in the general population.
- Flaviviruses, especially dengue virus and Japanese encephalitis virus, are associated with increased risk of fetal loss (miscarriages and stillbirths).
- Zika virus and Venezuelan equine encephalitis virus are teratogenic, causing fetal complications such as microcephaly for Zika virus.
- Intrapartum arbovirus mother-to-child transmission, especially of chikungunya virus, might cause severe neonatal disease, such as encephalitis.
- The actual burden of arbovirus infections during pregnancy and the true incidence of adverse fetal outcomes remain unknown.

Epidemiology and vectors

The main arboviruses causing human diseases are listed in tables 1–3. Transmission of human arboviruses

See Online for appendix

	Geographical 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* spp)	No data	No data	No data
Chikungunya virus (CHIKV)	America (tropical areas), Africa, Asia, Australia, Indian Ocean	Mosquito (*Aedes* spp)	No increased risk of severe maternal infection	Transmission documented, low incidence; miscarriages documented in three (2%) of 678 participants in one study and no increase in number of stillbirths, prematurity, or malformation[8]	Documented; transmission rate of 28–49%[8,12] with severe neonatal infection (encephalopathy) in 53% of newborns in one study;[8] severe neonatal infection with encephalopathy shown in four studies[8,13-15]
Eastern equine encephalitis virus (EEEV)	America (North, Central, and South)	Mosquito (*Culiseta* spp)	No data	No data	No data
Mayaro virus (MAYV)	South America	Mosquito (*Aedes* spp)	No data	No data	No data
O'Nyong-nyong virus (ONNV)	Central Africa	Mosquito (*Anopheles* spp)	No data	Transmission uncertain; two miscarriages reported, but link to infection unknown (fetuses untested)[16]	No data
Ross River virus (RRV)	Australia, Pacific area	Mosquito (*Aedes* spp and *Culex* spp)	No data	Transmission documented; 3% asymptomatic transmission in a case series[17]	No data
Sindbis virus (SINV)	Africa, Asia, Australia, Europe (Norway, Sweden, and Finland)	Mosquito (*Aedes* spp, *Culex* spp, and *Culiseta* spp)	No data	Transmission uncertain; two stillbirths reported, including one following overt maternal infection at 32 weeks of gestation (fetuses untested)[18]	No data
Venezuelan equine encephalitis virus (VEEV)	America (Central and South)	Mosquito (*Culex* spp)	No data	Transmission documented, incidence unknown; virus documented in the brains of ten aborted fetuses;[19] developmental brain lesions in infants born from mothers infected at 13–36 weeks of gestation[20]	No data
Western equine encephalitis virus (WEEV)	America (North, Central, and South)	Mosquito (*Aedes* spp and *Culex* spp)	No data	No data	Documented, incidence unknown; three cases with severe encephalitis, one of which was fatal[21,22]

Miscarriages refer to fetal losses before 28 weeks of gestation. Stillbirths refer to fetal losses at 28 weeks of gestation or later.

Table 1: **Classification, maternal risk, and consequences of mother-to-child transmission of major alphaviruses**

involves three factors: a vertebrate reservoir, blood-sucking arthropods that act as biological vectors, and human hosts that can be infected as spillover events and who become a secondary reservoir in urban settings, such as for dengue virus, chikungunya virus, and Zika virus.[3,4] A wide variety of mosquito, tick, midge, and sandfly species are vectors for arboviruses, although only a few specific vectors are usually implicated for a particular arbovirus.

The distribution of arboviruses depends on the type, competence, and distribution of their respective vectors; geographical and climate variables; and the presence of enzootic cycles that act as amplifying reservoirs (figure 1).[56] As a result, the geographical distribution of arbovirus species is uneven and constantly changing. Some arboviruses are, at least so far, restricted to specific regions—for example, Japanese encephalitis virus is present in Asia whereas yellow fever virus is absent (although its sequence has recently been identified in a patient in Africa[57]),[58] dengue virus circulates in all tropical and subtropical areas, and tick-borne encephalitis virus is only present in central and eastern Europe and Asia.[59,60] Other arbovirus species have emerged or re-emerged as local outbreaks and then spread on a large scale. For example, West Nile virus emerged in eastern USA in 1999 and then spread to the west coast of the USA during the next 5 years; chikungunya virus spread from east Africa to the Indian Ocean and Asia (2004–07) and emerged in the Americas in 2014; and Zika virus, which originated in Africa, emerged in the Pacific Islands in 2008, and reached South and Central America in 2015, from where the outbreak 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, such as chikungunya virus in Italy in 2007.[61] Other arboviruses remain geographically limited, such as Kyasanur Forest disease virus in Karnataka state in India (where most cases have been reported), and Oropouche virus, Mayaro virus, or Cache Valley virus in the Americas, but these viruses might spread if conditions that promote transmission arise.[62] For example, in Egypt, the Aswan Dam construction was responsible for major vector amplification of Rift Valley fever virus that led to abortion storms in cattle and the subsequent spread of this epizootic virus to humans.[63] Climate change has also been proposed as a possible trigger of Bunyaviridae spreading around the Mediterranean basin, and of Crimean–Congo haemorrhagic fever virus being found in Madrid, Spain, in August, 2016.[64,65] These unexpected cases illustrate the possibility of arbovirus emergence outside of the tropics if the right conditions are met. The factors responsible for the present global arbovirus outburst have been extensively studied[3] and include a combination of anthropogenic factors (increased human transportation, deforestation, urbanisation, rainwater storage, poor sanitation conditions), inefficient vector control and resistance to insecticides, and climate change (including El Niño and global warming).[56] These

	Geographical area	Main vectors	Maternal risk	Antenatal consequences of mother-to-child transmission	Perinatal consequences of mother-to-child transmission
Dengue virus (DENV)	Tropical and subtropical areas worldwide	Mosquito (*Aedes* spp)	Documented risk of severe infection; increased risk of haemorrhagic fever/shock syndrome compared with non-pregnant women of reproductive age (odds ratio 3·38, 95% CI 2·10–5·42)[11,23-26]	Transmission documented; increased fetal losses in the first half of pregnancy (data from multiple cohorts, substantiated by a meta-analysis)[27-29]	Documented, incidence unknown; severe neonatal infection with sepsis-like symptoms and acute respiratory distress reported in case reports[30,31]
Japanese encephalitis virus (JEV)	Asia, Australia	Mosquito (*Culex* spp)	No data	Transmission documented and severe; incidence unknown; fetal losses documented only in maternal infections occurring <22 weeks of gestation[32]	No data
Kyasanur Forest disease virus (KFDV), Alkhurma haemorrhagic fever virus (AHFV)	Asia (Middle East, India, southeast, and western Asia)	Tick (*Haemophysalis* spp)	No data	No data	No data
Murray Valley encephalitis virus (MVEV)	Australia, Papua New Guinea	Mosquito (*Culex* spp)	No data	No data	No data
Powassan virus	North America	Tick (*Ixodes* spp)	No data	No data	No data
Saint Louis encephalitis virus (SLEV)	America (North and Central)	Mosquito (*Culex* spp)	No data	No data	No data
Tick-borne encephalitis virus (TBEV)	Northern Europe and northern Asia (in a belt extending from eastern Europe to Japan)	Tick (*Ixodes* spp)	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* spp)	No data	Transmission documented; extremely rare; one case of congenital chorioretinitis and encephalitis after maternal infection at 27 weeks of gestation;[33] no significant increase in fetal losses or adverse long-term neurological outcome in US cohort studies[34-36]	Uncertain; two cases with encephalitis that developed 6–10 days after birth (maternal symptoms 21–6 days before delivery, no documentation of viral infection at birth);[35] one 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* spp or *Haemagogus* spp)	No data	Transmission documented; extremely rare; two cases of fatal and maternal infection at 4–5 months of pregnancy with lesions compatible with yellow fever virus in the fetuses[37]	Documented, probably extremely rare; one report of fatal neonatal infection (maternal symptoms onset 3 days before delivery)[38]
Zika virus (ZIKV)	South Pacific area, Latin America, Caribbean, USA (Florida and Puerto Rico)	Mosquito (*Aedes* spp)	..	Transmission documented; incidence of 1–13% brain abnormalities at birth;[39,40] 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] and impaired postnatal neurological development with poor cranial growth, irritability, pyramidal or extrapyramidal symptoms, and epilepsy[46]	Documented; probably extremely rare; two French Polynesian case reports of possible perinatal transmission (one asymptomatic, one with mild rash)[47]

Miscarriages refer to fetal losses before 28 weeks of gestation. Stillbirths refer to fetal losses at 28 weeks of gestation or later.

Table 2: **Classification, maternal risk, and consequences of mother-to-child transmission of major Flaviviridae viruses**

conditions favour contacts between permissive hosts and competent vectors, as well as also facilitating vector amplification and extension beyond tropical latitudes. Selection of virus variants, through emergence of isolates with enhanced virulence, enhanced vector or vertebrate host fitness, or both, might also be involved.[3]

Maternal clinical presentation

As in the non-pregnant host, typical presentations of arbovirus infections in pregnant women vary according to the virus involved, but they do share common features. Incubation is short, typically less than a week after the arthropod bite. Three main patterns are observed, which might overlap: fever and flu-like symptoms with or without rash (eg, Zika virus, dengue virus, the arthogenic alphaviruses chikungunya virus and Ross River virus, Oropouche virus, and West Nile virus); encephalitis or meningoencephalitis (eg, Japanese encephalitis virus, tick-borne encephalitis virus, Saint Louis encephalitis virus, Venezuelan equine

	Geographical area	Main vectors	Maternal risk	Antenatal consequences of mother-to-child transmission	Perinatal consequences of mother-to-child transmission
Crimean-Congo haemorrhagic fever virus (CCHFV)	Europe (southeast and eastern), Africa, Middle East, countries south of the 50th parallel	Midge (*Culicoides* spp); tick (>30 species involved)	Documented increased risk of severe infection: increased mortality (34%[48])	Transmission documented, incidence unknown; four miscarriages at 4–19 weeks of gestation (fetuses untested);[48] stillbirths with maternal death[48,49]	Documented, incidence unknown; one case of documented fatal neonatal infection[50]
La Crosse virus (LACV)	North America (mid-western and eastern)	Mosquito (*Aedes* spp)	No data	Transmission documented, incidence unknown; one asymptomatic mother-to-child transmission documented serologically in cord serum, after a maternal infection at 21 weeks of gestation[51]	No data
Oropouche virus (OROV)	America (Central and South)	Midge (*Culicoides* spp)	No data	No data	No data
Rift Valley fever virus (RVFV)	Africa, Middle East, Asia	Mosquito (*Aedes* spp, *Culex* spp, and *Anopheles* spp)	No data	Transmission documented; increased risk of miscarriage in a cross-sectional study comparing miscarriages in pregnant patients with documented Rift Valley fever virus (15 [54%] of 28 participants) *vs* pregnant women with documented chikungunya virus infection (12 [12%] of 103)[52]	Documented, incidence unknown; two symptomatic cases (infants born to mothers who were 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 Korea)	Not completely elucidated; evidenced in ticks (*Haemaphysalis* spp)	No data	No data	No data
Tahyna virus (TAHV)	Europe, Africa, Asia	Mosquito (*Culex* spp)	No data	No data	No data
Toscana virus (TOSCV)	Europe	Sandfly (*Phlebotomus* spp)	No data	No data	No data
Colorado tick fever virus (CTFV)	North America	Tick (*Dermacentor* spp)	No data	Transmission uncertain; two 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	Sandfly (*Sergentomyia* spp)	No data	No data	No data

Miscarriages refer to fetal losses before 28 weeks of gestation. Stillbirths refer to fetal losses at 28 weeks of gestation or later.

***Table 3*: Classification, maternal risk, and consequences of mother-to-child transmission of major Bunyaviridae, Reoviridae, and Rhabdoviridae arboviruses**

encephalitis virus, western and eastern equine encephalitis viruses, La Crosse virus, West Nile virus, Toscana virus, Colorado tick fever virus, and Chandipura virus, and less commonly, dengue virus, chikungunya virus, and Zika virus); or haemorrhagic fever (eg, yellow fever virus, Rift Valley fever virus, Crimean–Congo haemorrhagic 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 >85% of cases), yellow fever virus,[66] and the Asian lineage of Zika virus (symptomatic in 50% of cases).[67] Generally, mortality varies according to the causative agent and clinical presentation, and is reported in up to 30% of infections with Crimean–Congo haemorrhagic fever virus, Japanese encephalitis virus, yellow fever virus, and dengue virus infections that are complicated by haemorrhagic fever/shock syndrome. Anecdotal cases of deaths have been reported in other arbovirus infections. 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, causes persisting neurological disabilities in more than 30% of surviving patients.[60] Arthrogenic alphaviruses can also cause less severe complications, such as long-lasting articular disease (associated with chikungunya virus, Mayaro virus, or Ross River virus infection) or persisting fatigue after clearance of dengue virus.

Until recently, pregnancy was not identified in epidemiological studies as a specific risk factor for severe arbovirus infection, by contrast with other infections such as influenza, varicella, measles, and malaria that are notably more severe during pregnancy. The two notable exceptions are dengue virus and Crimean–Congo haemorrhagic fever virus, which are both associated with life-threatening haemorrhagic complications during pregnancy.[68,69] Indeed, arbovirus haemorrhagic complications not only increase maternal mortality, but are also associated with increased frequencies of caesarean section and post-partum haemorrhages with additional life-threatening consequences in infected mothers.[50,70] A substantial increase in severe dengue (ie, dengue haemorrhagic fever/shock syndrome) has been reported in pregnant women in Brazil, especially during the second and third trimesters, as compared with non-pregnant women of reproductive age (odds ratio [OR] 3·38, 95% CI 2·10–5·42).[11] Mortality was 22% in pregnant Sudanese women diagnosed with dengue haemorrhagic fever/shock syndrome,[71] and 34% in pregnant women with Crimean–Congo haemorrhagic fever, which is probably higher than in the general population.[48,49]

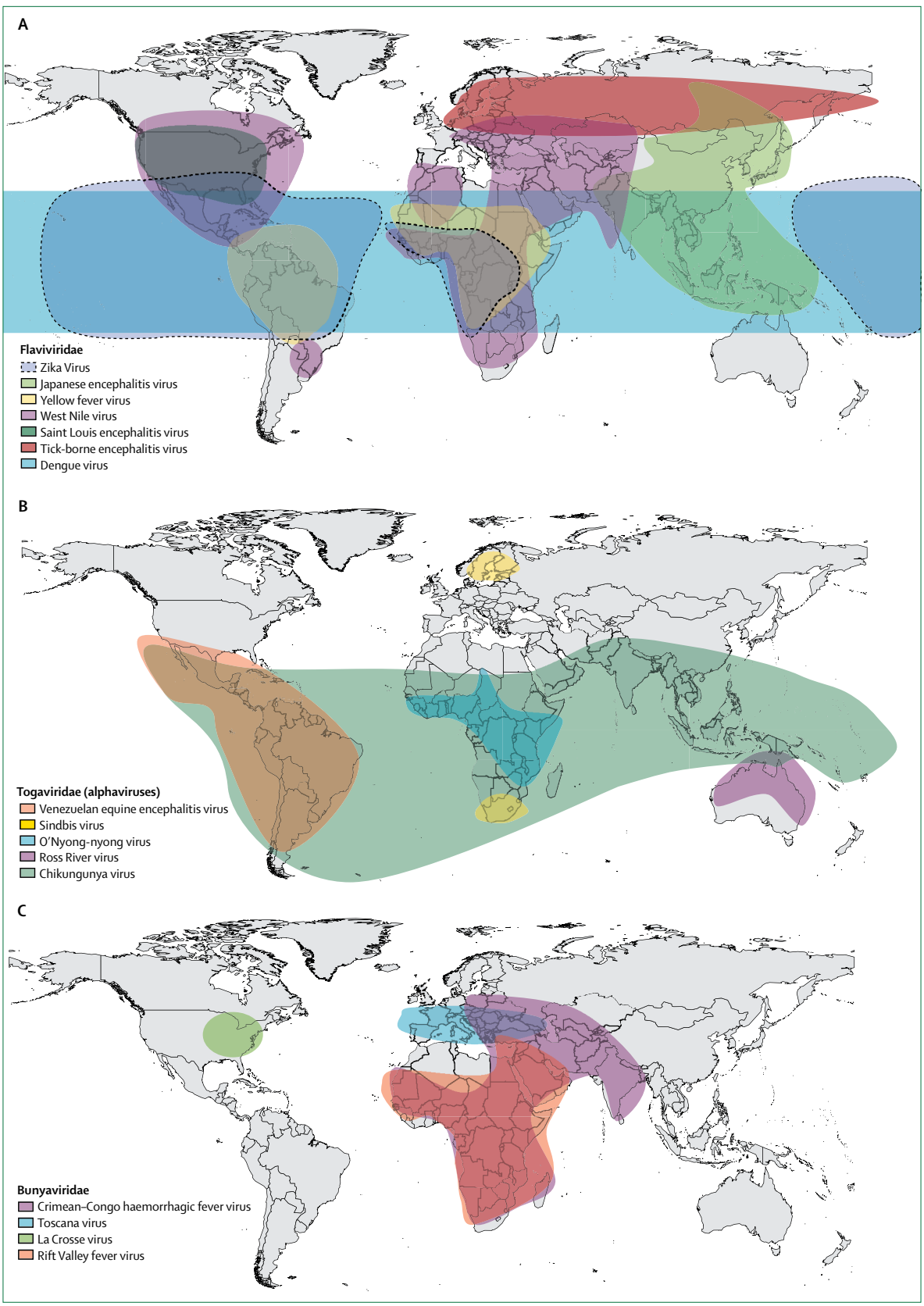

Figure 1: **World distribution of major arbovirus infections**

Fetal and neonatal consequences of maternal infection

When maternal arbovirus infection is reported, obstetric follow-up should include assessment of placental function, and fetal vitality and growth, with careful ultrasound detection and characterisation of fetal developmental defects and of clinical and radiological neonatal abnormalities. Few arboviruses have been studied in detail with regard to their direct and indirect effects on the fetal–placental unit, and almost all available data are derived from the arboviruses of the Togaviridae and Flaviridae families. The fetal and neonatal complications range from fetal losses (miscarriages <28 weeks of gestation and stillbirths thereafter,[9] mostly associated with dengue virus, Japanese encephalitis virus, Zika virus, and Venezuelan equine encephalitis virus); premature delivery and low birthweight for gestational age (mostly associated with dengue virus); developmental defects and teratogenicity (associated with Zika virus and Venezuelan equine encephalitis virus); perinatal infection (defined as neonatal infection occurring either on intrapartum contamination or after late antepartum contamination, within the last days of pregnancy; associated with chikungunya virus and, to a lesser extent, dengue virus,[12,27,29,30,72] with case reports for yellow fever virus,[38] Zika virus,[42,47] and western equine encephalitis virus).[21,22]

Dengue virus is associated with a substantial risk of adverse fetal outcome. In a meta-analysis, Paixão and colleagues[29] showed that symptomatic dengue is associated with an increased risk of miscarriage (OR 3·51, 95% CI 1·15–10·77), stillbirth (crude relative risk 6·7, 95% CI 2·1–21·3), preterm birth (OR 1·71, 1·06–2·76), and low birthweight for gestational age (1·41, 0·90–2·21). Fetal losses after dengue virus infection have been reported until 25 weeks of gestation.[27] Fetal losses correlate with the severity of maternal symptoms, and rates of fetal loss in mothers with asymptomatic infection do not differ from those in uninfected pregnant women.[29] Data from Brazil suggest that maternal sickle cell disease, a highly prevalent genetic trait in Latin America and Africa, might increase dengue-associated risk of fetal loss.[73] It is unknown whether serotype has an effect on fetal loss. Perinatal dengue virus transmission has also been reported in women with symptoms occurring around 10 days before delivery, yet its actual incidence is unknown.[30,74] Maternal antibodies specific to dengue virus and passively transmitted to the fetus confer protection for neonates towards the dengue serotpye it is directed against, but also increase the risk of severe infection involving another dengue virus serotype. This phenomenon, referred to as antibody-dependent enhancement, results from antibody-mediated facilitation of virus infection of cells expressing Fc receptors.[75,76]

Japanese encephalitis virus has been reported to cause miscarriages up to 22 weeks of gestation.[77] In the only case series reported,[32] all maternal infections occurring within 22 weeks of gestation were complicated with fetal losses, whereas all those occurring thereafter were not.

Congenitally acquired encephalitis and chorioretinitis after maternal infection with West Nile virus at 27 weeks of gestation was reported in one case,[33] but results from subsequent large epidemiological studies[78,79] showed no increased risk for fetal infection or demise, nor any long-term neurological impairment in children born from mothers infected with West Nile virus during their pregnancy.

Venezuelan equine encephalitis virus is associated with frequent miscarriages, stillbirths, and premature deliveries, as observed during the large outbreaks in Venezuela in 1962 and 1995. Autopsies were done in ten cases, and Venezuelan equine encephalitis virus was found in the brains of all aborted fetuses.[2,20] Infants born to mothers who had Venezuelan equine encephalitis between 13 and 36 weeks of gestation also had neurological disorders, which led to the classification of Venezuelan equine encephalitis virus as the first teratogenic arbovirus.[80] These infants presented with fatal cerebral lesions ranging from extensive necrosis to hydranencephaly, with neuronal and astrocyte abnormalities.[80] Of note, Venezuelan equine encephalitis virus is an alphavirus that belongs to the Togaviridae family, which also includes rubella virus, a notorious teratogenic virus associated with a severe congenital syndrome.

Asian lineage Zika virus has emerged as a major arbovirus since 2015, when medical observations and experimental investigations led to the conclusion that Zika virus is a major teratogenic arbovirus, and the only one so far of the Flaviviridae family in human beings. Until 2015, Zika virus was considered as causing only a benign illness in rural areas of Africa, where it is endemic, before it emerged in Micronesia (where 5000 people were affected) and French Polynesia (where 100 000 were affected), and then spread to Latin America on a large scale, where the high incidence of Zika virus in a non-immune population living in a highly medicalised area led to the identification of its association with fetal complications.[39,81] Data collected in Brazil and retrospective analysis of data from French Polynesia showed the temporal and geographical association between Zika virus infection in pregnant women and fetal losses, growth restriction, and fetal and neonatal developmental defects, initially identified as microcephaly.[39,82] Congenital Zika syndrome now includes microcephaly, which can be associated with neurological abnormalities, including eye lesions (such as malformations, optic neuritis, chorioretinal scarring, and atrophy), hearing loss, and cranio-facial and musculoskeletal lesions that probably result from the fetal akinesia deformation sequence (ie, arthrogryposis, lung hypoplasia, flat midface, scoliosis, and limb deformations).[83,84] Autopsy data from babies with congenital Zika syndrome have shown cerebral ventriculomegaly, lyssencephaly, cerebellar hypoplasia, and agyria.[85–88] Microscopic brain lesions

include microcalcifications, gliosis, neuronal and glial cell degeneration and necrosis located at the subcortical–cortical transition, perivascular infiltrate of T cells and B cells in the subcortical white matter, and Wallerian degeneration of the long descending tracts.[88] Reduced placental function with fetal growth restriction and fetal loss is also reported when maternal infection occurs up to 32 weeks of gestation.[42] The frequency of brain abnormalities at birth in infants born from mothers with Zika virus infection is estimated to be between 1% and 13%,[39,40] and 26 (6%) of 442 fetuses or infants in a US cohort had birth defects potentially related to Zika virus.[43] The peak of fetal susceptibility to congenital Zika syndrome appears to be the first trimester of pregnancy, although 14% of infants with Zika virus-associated microcephaly in a Brazilian cohort had maternal infection in the second trimester; brain calcification was seen in a fetus infected at 34 weeks of gestation and haemorrhages were seen in a fetus infected at 39 weeks of gestation.[42] The long-term postnatal neurological consequences of fetal infection with Zika virus remain to be fully determined. Results from a preliminary study of 48 Brazilian infants[46] suggested poor cranial growth, irritability, pyramidal and extrapyramidal symptoms, and epilepsy at up to 8 months of age, including in children without microcephaly at birth.

Neonatal infection with chikungunya virus can occur via intrapartum contamination, and is now recognised as a major complication of maternal chikungunya infection.[8] Vertical transmission occurs in up to half of mothers who are viraemic during labour.[12] Neonatal symptoms develop between 3 and 7 days of life, and range from mild presentation (43%) to severe infection with encephalitis (53%) that requires intensive care.[8] Fever and acute respiratory distress have also been reported.[12] This presentation is hardly distinguishable from bacterial sepsis, and diagnosis is challenging when maternal infection has not been diagnosed. Neurological complications of neonatal chikungunya virus disease can have severe effects on postnatal neurological development: development quotient (median 86 *vs* 100; $p<0·001$) at the age of 2 years is lower, and moderate to severe global neurodevelopmental delays are more frequent (51% *vs* 15%; $p<0·001$) in infants with perinatal infection compared with uninfected matched controls.[89]

By contrast with severe fetal outcomes associated with chikungunya virus, mother-to-child transmission of Ross river virus has been reported as asymptomatic, and is not associated with neonatal pathology.[17]

Pathophysiology

Mechanisms associated with increased disease severity in mothers with dengue and Crimean–Congo haemorrhagic fever are unknown, although the effect of utero–placental haemorrhages might be involved, especially in low-resource countries, where access to transfusion and surgery is limited. Fetal and neonatal complications can result from four complementary processes: acute fetal distress in the context of a severe maternal infection impairing maternal haemodynamics, and therefore placental and fetal oxygenation; placental arbovirus infection without fetal infection, but with subsequent reduction of blood flow to the fetus; fetal infection through virus crossing of the placental barrier; and neonatal infection via labour-associated placental breaches (figure 2).[90]

Maternal haemodynamic changes might affect placental perfusion and thereby the developing fetus, as has been suggested for dengue virus infection.[73] Indeed, histopathological analyses of placentas collected at delivery from mothers with dengue virus infection have shown hypoxic lesions with villous stroma oedema, and infarcted and pre-infarcted areas in 19 of 24 cases, including eight from mothers who did not report overt shock syndrome.[73] These maternal haemodynamic changes are also the most likely scenario accounting for fetal losses in severe Crimean–Congo haemorrhagic fever, although this has not been 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 mothers with dengue. Indeed, results from a histopathological study[72]

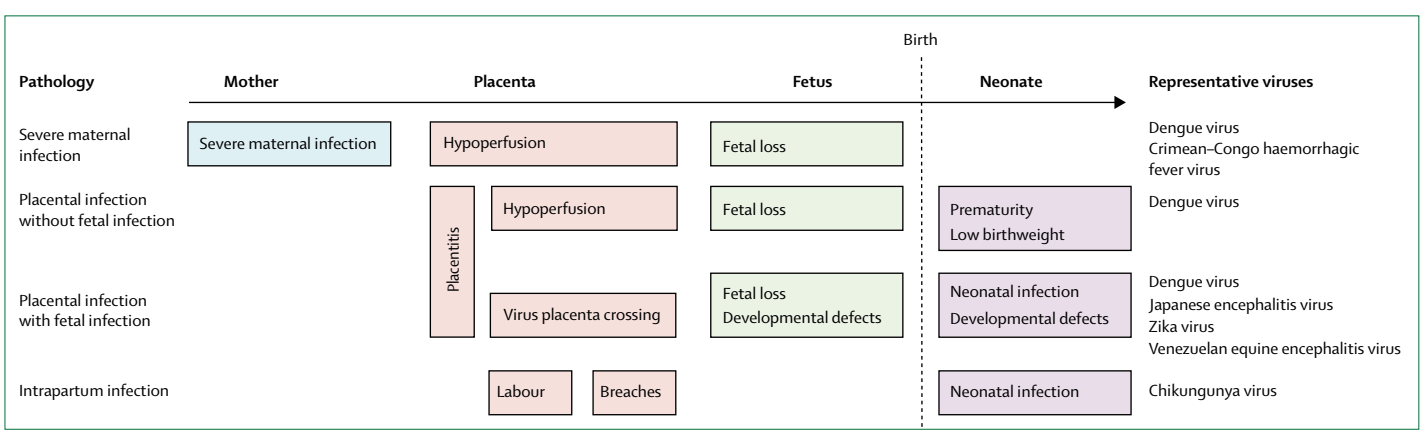

Figure 2: **Patterns of pathophysiological events associated with adverse fetal or neonatal outcomes**

also showed choriodeciduitis and villitis; immunostaining showed viral antigens in the decidual cells, trophoblasts, and villous stroma cells in 22 of 24 cases, of which ten cases had overlapping histological lesions.

Placental arbovirus infection can also lead to antepartum mother-to-child transmission, which can either be asymptomatic or lead to fetal death or developmental defects (teratogenicity). The association of mother-to-child transmission with fetal death has been poorly studied in human beings and is only documented for Zika virus and Japanese encephalitis virus, but this association has been reported in other mammals for many arboviruses, such as Venezuelan equine encephalitis virus in mice and mares,[91,92] western equine encephalitis virus in rhesus macaques,[93] Ross river virus in mice,[94] Japanese encephalitis virus in swine, West Nile virus in mice,[95] and Rift Valley fever virus in ruminants.[8,96] The events and timing associated with fetal and litter losses are far from being fully elucidated. The earlier the maternal infection occurs, the more severe the fetal consequences are, as shown in mice for West Nile virus and Japanese encephalitis virus, and in human beings for Japanese encephalitis virus.[95,97]

In veterinary medicine, developmental defects have been observed in offspring after epizootic events, which provided the first basis for incriminating arboviruses as teratogenic, long before the ongoing Zika virus outbreak. Developmental defects include brain lesions, regardless of the arbovirus family involved, which is in line with the observation that most other vertically transmitted pathogens are also neurotropic, such as rubella virus, bacteria such as *Listeria monocytogenes* and *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 for other animal arboviruses that have not yet been identified in human beings, such as Wesselsbron virus (calves; Flaviviridae), bovine viral diarrhoea virus (calves; Flaviviridae) or Banzi virus (sheep; Flaviviridae), Schmallenberg virus (calves; Bunyaviridae) or Akabane virus (goats and calves; Bunyaviridae), or blue-tongue virus (calves; Orbiviridae).[98–101] In human beings, only Venezuelan equine encephalitis virus and Zika virus are teratogenic. Venezuelan equine encephalitis virus was first identified in 1977 in a rhesus monkey model of infection to cause microcephaly and hydrocephaly,[102] but detailed pathophysiological data are not available and the mechanisms of viral crossing of the placental barrier and teratogenicity have not been elucidated. Results from experiments in rats showed the presence of viral antigens on the cytotrophoblasts and syncytiotrophoblasts.[103] By contrast, the pathogenicity of Zika virus has been extensively studied since 2015, in the context of its massive dissemination in Latin America. Results from clinical, experimental, and epidemiological studies have shown the teratogenicity of Zika virus, on the basis of temporality, biological plausibility, strength of association, exclusion of alternative explanations, animal experiments, consistency, and analogy with other teratogenic pathogens.[81] Zika virus has unique properties that can account for the Zika virus congenital syndrome: it is able to cross the placental barrier, multiply in the placenta and disseminate to the fetus, and target 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 extravillous cytotrophoblast but not the mature syncytiotrophoblast.[104,105] How Zika virus reaches these extravillous cytotrophoblastic cells, which are not directly accessible from the maternal blood, remains to be elucidated. In the placenta, Zika virus can multiply in resident macrophages called Hofbauer cells, as shown by histological data and results from experiments in explants and cultured cells.[104,106] The virus might replicate in these cells and in infected placental endothelial cells, thus favouring its release in the fetal circulation.[83] In the fetus, Zika virus is neurotropic, with higher viral RNA titres found in the brain than in the lungs, spleen, and liver.[88,107,108] 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 only flavivirus that is transmitted vertically and that can specifically infect cortical progenitors. Dengue virus antibodies have been shown to cross-react with Zika virus in vitro, and thereby enhance Zika virus infection; this could have important clinical consequences (since both viruses are highly prevalent in Latin America), as well as for the development of vaccines against both viruses.[109]

Intrapartum contamination without actual placental infection is a direct consequence of maternal viraemia and fetal or neonatal susceptibility to a given arbovirus species. Such contamination has been well documented for chikungunya virus, which, by contrast with Zika virus, is not able to infect the placenta.[8,10] Chikungunya virus is therefore not transmitted to the fetus in the absence of placental breaches, which allow a transfer of maternal blood to the fetal circulation. Indeed, the virus cannot be detected as replicating in the placentas of viraemic mothers, and human syncytiotrophoblastic cell lines are refractory to infection in vitro.[10] This finding was substantiated by findings from experimental infections in a model of pregnant interferon-α/β-receptor knockout mice, in which placentas constitute an absolute barrier to chikungunya virus that protect highly susceptible fetuses from infection, despite high maternal viraemia.[10]

Diagnosis

Procedures to diagnose arbovirus infections in pregnant women do not differ from those used in the general population. Biological abnormalities—including lymphopenia, thrombocytopenia, and increased serum transaminase levels—can mimic a pregnancy-associated complication called HELLP syndrome (which can precede eclampsia and is characterised by haemolysis, elevated liver enzymes, and low platelet count) and therefore delay diagnosis. Virological diagnosis relies on

arbovirus-specific reverse-transcriptase-PCR assays in blood or cerebrospinal fluid, and on serological assays (IgM detection, IgG seroconversion, or a 4-fold increase in IgG titres on sera collected at intervals of 10–14 days). Reverse-transcriptase PCR in the blood is limited to the diagnosis of arboviruses that cause high viraemia during the first few days of symptoms, such as West Nile virus, dengue virus, chikungunya virus, and Zika virus.[66] Detection of virus-specific IgM in the cerebrospinal fluid can also be done.[110] Zika virus RNA is also detectable in the urine for 14–21 days.[111]

The diagnosis of fetal infection is based on reverse-transcriptase PCR of amniotic fluid or fetal blood to prove mother-to-child transmission. The added value of antenatal screening for arboviruses has not been precisely evaluated, and the procedure might actually favour mother-to-child transmission. The exception is antenatal screening for Zika virus in view of its notable teratogenic effect; amniocentesis is considered on an individual basis when pregnancy termination would be medically considered and ethically and legally authorised.[112] Clinicians should be aware that biological samples with suspected or demonstrated level-3 pathogens (ie, most arboviruses in non-endemic areas) and level-4 pathogens (such as Crimean–Congo haemorrhagic fever virus) require adequate management in authorised facilities.

Prevention of maternal infection

Vector control and limitation of contact with arthropods is key to preventing arbovirus infection. General protective measures for pregnant women are similar to those for the general population, such as covering exposed skin, checking for tick bites (eg, for Crimean–Congo haemorrhagic fever virus), and using window and door screens, bednets, and, if possible, air-conditioning. The use of insect repellent at the recommended dose is considered safe for pregnant women.[113,114]

Commercial vaccines are available against Japanese encephalitis virus, tick-borne encephalitis virus, and yellow fever virus. There are 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 in view of the absence of large cohort studies, these vaccines should only be administered after careful individual risk–benefit assessment.[115] 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, WHO recommends its administration in pregnancy if travel to an endemic area is unavoidable.[116] This recommendation is based on the apparent safety of yellow fever vaccine in pregnant women in large-scale vaccination campaigns in Africa and Brazil, and on the severity of the disease and persisting burden in unvaccinated populations.[117,118] The first live-attenuated dengue vaccine was approved in Mexico in 2015.[119] The lack of available data in pregnant women and the usual restrictions on live vaccines in pregnancy preclude, for now, the use of a live-attenuated dengue vaccine in this setting. A formalin-inactivated vaccine for Rift Valley fever virus and an inactivated vaccine against Kyasanur Forest disease virus have also been developed but are not widely available, and there are no data on their use during pregnancy.[120] There is still no commercially available vaccine against chikungunya virus. Passive immunisation with polyclonal immunoglobulins is effective in preventing Crimean–Congo haemorrhagic fever virus, Rift Valley fever virus, and West Nile virus infections, but this approach has not been studied in pregnant women.[121–123] Although the consensus is that a vaccine to prevent Zika virus-associated fetopathy is crucial, testing the efficacy and safety of such a vaccine in pregnant women is challenging, because the risks associated with Zika virus that are to be prevented by vaccination should outweigh the 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 is considered useful in some extremely severe cases, such as infection by Crimean–Congo haemorrhagic fever virus and Rift Valley fever virus, but its teratogenic effect precludes its use during pregnancy, except in life-threatening maternal infections.[124] BCX4430, an adenosine nucleoside analogue with broad-spectrum antiviral properties against RNA viruses, is being investigated (ClinicalTrials.gov, NCT02319772). It has shown in-vitro activity towards Filoviridae, Bunyaviridae, and Flaviviridae, including mosquito-borne species (yellow fever virus, Japanese encephalitis virus, dengue virus type 2, West Nile virus, and African and Asian lineages of Zika virus) and tick-borne species (tick-borne encephalitis virus, Kyasanur Forest disease virus, and Louping ill virus).[125] It is active in vitro and in a mouse model of Zika virus infection, and is being studied in phase 1 trials in healthy volunteers, with promising pharmacokinetics and tolerance.[126,127]

Some existing drugs with potential antiviral effects can also be repurposed. Ivermectin is an antihelmintic drug with antiviral properties that inhibits replication of flaviviruses by targeting the activity of NS3 helicase.[128] A clinical trial in Thailand (NCT02045069) is assessing the efficacy of ivermectin to treat dengue. If shown to be beneficial, this approach would lead to new opportunities for the treatment of maternal dengue, because ivermectin is known to be safe during pregnancy.[129] Azithromycin is a macrolide that is considered safe to use during pregnancy and has been shown to have an antiviral effect against Zika virus.[130]

Whole-genome RNA interference and CRISPR (clustered regularly interspaced short palindromic

repeat)–Cas9 screens have helped to identify multiple host pathways that could be targeted, for which antiviral development is underway.[131,132]

Therapeutic strategies for neonates

Passive immunotherapy by infusion of immunoglobulins can prevent mother-to-child transmission, as reported for hepatitis B. Immunoglobulins can reduce viral load and therefore the burden of neonatal infection.[133] Such strategies could be extremely promising in the field of arbovirus infections. Polyvalent immunoglobulins purified from plasma obtained from chikungunya-convalescent human donors are protective and curative in a mouse model.[134] Anti-chikungunya virus hyper-immunoglobulins are being assessed for their safety and efficacy in the prevention of mother-to-child transmission of chikungunya virus in neonates born to viraemic mothers (CHIKIVIG-01, NCT02230163). Similar approaches have been reported against West Nile virus but have not been assessed in pregnant women.[135]

Gaps in knowledge

Although many arboviruses are known to have adverse effects in pregnancy on both the mother and the child, the actual burden of arbovirus infections during pregnancy remains unknown and the true incidence of adverse fetal outcomes has not been assessed.[136] This knowledge gap results from a combination of epidemiological factors (coexistence of different arboviruses in the same geographical areas and present rarity of some arbovirus infections); medical factors, since most arbovirus infections can be asymptomatic; socioeconomic factors, considering the worldwide heterogeneity of health-care access for pregnant women and neonates, especially concerning availability of diagnostic procedures, of care-seeking behaviour for maternal symptoms or for fetal loss; and finally, methodological factors, because many studies do not have the statistical power to detect obstetric consequences in contexts of low or unknown arbovirus incidence.[19,137,138] Dedicated prospective studies based on large population data are urgently needed, along with the systematic reporting of sporadic cases, including imported cases in high-income countries. Sustainable and interconnected surveillance systems are mandatory to better assess epidemiological signals. Existing 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 of congenital arbovirus infections.

Pathophysiological mechanisms underlying arbovirus-associated maternal symptoms, 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 substantially within a 1 year window. Similar studies are now needed for other highly prevalent arboviruses, for which their effect on pregnancy has not been precisely characterised.

Finally, therapeutic trials dedicated to mother and child issues are urgently needed. Infectious diseases remain the most common cause of maternal death worldwide.[139] Improving the understanding of arbovirus infections in pregnancy and their medical management might help to reach two of the eight Millennium Development Goals set by the UN and the Bill & Melinda Gates Foundation: to improve maternal health and to reduce child mortality.

For more on the **Millennium Development Goals** see http://www.un.org/millenniumgoals

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 done replacing the generic term "arbovirus" with the name of each individual known arbovirus, such as "chikungunya", "Venezuelan equine", "Japanese encephalitis", and "dengue". The complete list of terms and search strategy are available in the appendix. We searched for papers published in English, French, Spanish, and German.

Contributors

CC and ML conceived the review. CC, TC, and M-CB reviewed the literature. CC and ML wrote the manuscript. All authors edited and approved the manuscript.

Declaration of interests

We declare no competing interests.

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