Vector-borne diseases in pregnancy

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***Abstract*:** Vector-borne infections cause a significant proportion of world-wide morbidity and mortality and many are increasing in incidence. This is due to a combination of factors, primarily environmental change, encroachment of human habitats from urban to peri-urban areas and rural to previously uninhabited areas, persistence of poverty, malnutrition and resource limitation in geographical areas where these diseases are endemic. Pregnant women represent the single largest 'at risk' group, due to immune-modulation and a unique physiological state. Many of these diseases have not benefitted from the same level of drug development as other infectious and medical domains, a factor attributing to the 'neglected tropical disease' title many vector-borne diseases hold. Pregnancy compounds this issue as data for safety and efficacy for many drugs is practically non-existent, precluding exposure in pregnancy to many first-line therapeutic agents for 'fear of the unknown' or overstated adverse pregnancy-foetal outcomes. In this review, major vector-borne diseases, their impact on pregnancy outcomes, current treatment, vaccination and short-comings of current medical practice for pregnant women will be discussed.

Keywords: neglected tropical diseases, pregnancy, vector-borne diseases

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Introduction

Vector-borne diseases have experienced a rise in recent years due to a number of factors globally. Rising global temperatures, the globalisation of human kind and encroachment of urban areas on previously natural habitats.[1] Approximately 17% of all infectious diseases are caused by vector-borne diseases, resulting in over 700,000 deaths annually. Just over 50% of the world's population are at risk at any time to these vector-borne diseases.[2] Those spread by vectors within the Insecta kingdom, including mosquitos, ticks and flies, are the focus of this review.

Mosquito-borne diseases predominately affect the southern hemisphere and cause by far the largest burden on mortality, quality of life, social, financial and economic burden globally.[3] Hard-shell tick-borne illnesses like Lyme disease affect temperate areas of the northern hemisphere, are less well defined but are a growing cause of morbidity internationally.[4,5] Soft shell ticks are present on all continents globally, relapsing fever borreliosis has been shown to be associated with foetal loss as high as 475 per 1000 in some sub-Saharan countries.[6] 'Neglected tropical diseases' spread primarily by flies, like Chagas disease, filariasis, leishmaniasis and Carrion's disease, are highly treatable and have a staggering impact on global health.[7] Rickettsial infections, which affect all habitable continents, have also been associated with significant morbidity,[8] have a number of vectors and can have particularly poor outcomes in pregnancy, possibly due to their affinity for vascular endothelial cells and micro-thrombosis of placental vasculature.

Pregnant women represent the single largest vulnerable group within human populations. This is due to both immune suppression in pregnancy and the gravity of an individual infection to impact on not one but two human lives. As pregnancy progresses, rising estradiol/progesterone, reducing CD4/CD8 cells, decreasing cytotoxic T cells and a shift from Th1 to Th2 have all been proposed to be important for susceptibility to

infections.[9] It has been proposed that pregnancy is a state of immune modulation rather than suppression.[10] Vector-borne infections impose a large burden on women of childbearing age worldwide. For many of these diseases, the complex interactions between mother, infant and the placenta are poorly understood.

Infections in newborns may cause classic, well-recognised syndromes like congenital zika syndrome, may be transient and self-limiting like yellow-fever, or long lasting as in chikungunya, or have occult beginnings and emerge later in life as we see with Chagas disease.[11–13] The timing of such infections in utero may determine the extent of infection and outcome to the unborn child. Thus, infections in pregnancy can have a wide variety of outcomes, depending on the timing of infection, the type of infection, the interaction of the infecting organism with the immune system and indeed certain host factors.

The main adverse events of infections in pregnancy include pre-eclampsia and HELLP (haemolytic anaemia, low platelets, elevated liver enzymes) syndrome, low foetal birth weight, congenital deformities, mother-to-child transmission of infection, preterm labour and delivery, spontaneous abortion and miscarriage, as well as peri-partum mortality of the mother or child.[11,14–16] Some infections can additionally be transmitted in the peri-partum period and post-partum through breastfeeding; such infections may manifest themselves immediately or in the later post-partum period, or even later in childhood and indeed extending into adolescence and adulthood.[17]

Regarding treatment choices, limitations in choice due to teratogenicity or a lack of data due to exclusion of pregnant women in drug studies is commonplace. These issues are compounded in resource-limited settings where access to treatment can be extremely limited or non-existent for a number of reasons, such as cost, geographic location and conflict. Vaccines are an additional option to prevent some of these infections, but, as with drug therapy, the known safety and efficacy of vaccines in pregnancy limits options.

Current paradigms of treatment are changing in recent times. Drugs like doxycycline and chloramphenicol, which have been avoided traditionally because of teratogenicity and grey baby syndrome, are now being re-reviewed as they are highly efficacious in a number of diseases, in particular rickettsial infections. The extent of their negative impact on the foetus is, in many cases, outweighed by their potential therapeutic benefit, which in some instances may be the viability of the foetus. The extent of doxycycline teratogenicity appears to have been initially overstated, and it can be prescribed when options are limited.[18] A summary of vector borne infections in pregnancy and current treatments is presented in Table 1.

Mosquito-borne infections in pregnancy

Climate change is currently leading to a rise in insecta species, including the mosquito *Aedes aegypti*. Over 300 million cases of mosquito-borne infections occur annually. Currently, no consensus exists on the exact trajectory of mosquito-borne diseases due to conflicting climatic factors, that is, rise in temperatures that may promote propagation of mosquitos to previously unaffected areas but may also have an impact on mosquito fecundity and virulence, as well as deforestation, pollution, agriculturalisation and urbanisation. These factors do inevitably lead to collapse of local ecosystems, and mosquitos may be more adaptive than other species.[3] Despite these conflicting issues, individually, some vector-borne diseases have flourished in recent years; for example, dengue has increased in incidence by 50 fold, and there has been an upsurge of zika and chikungunya virus infections in recent years.[19] *Ae. aegytpi* is endemic to many resource-limited countries across South America (SA), sub-Saharan Africa (SSA) and South East Asia (SEA) and harbours a number of diseases, including dengue, chikungunya, yellow fever and zika viruses. West Nile virus has also flourished, with an unrelenting march across North America, Europe and, to a lesser extent, Asia.[20,21]

Malaria

A total of 212 million people are infected annually with malaria, 92% of whom are living in the World Health Organisation (WHO)'s African Region. No significant reduction was seen compared with 2015 despite US$3.1 billion having been invested in malaria control and elimination efforts.[22] Currently, WHO global technical strategy goals of a reduction of incidence and deaths by 40% and elimination in 10 countries are off target.[23]

Table 1. Summary of vector-borne infections in pregnancy.

Infectious disease		Organism	Vector	Complications in pregnancy	Vertical transmission	Prophylaxis/ vaccination	Treatment in pregnancy
Mosquito borne							
Malaria	protozoa	*P. falciparum* *P. vivax* *P. ovale*	*Ae. aegypti*	Low endemicity: risk of severe infection with maternal/foetal loss[29] High endemicity: occult infections[30]	Accumulation in placenta but no vertical transmission	Doxycycline contraindicated ITNs RTS,S vaccine in development[25]	1T: Primaquine + clindamycin[33] 2–3T: ACT IPTp (sulfadoxine-pyrimethamine)[33]
Dengue	flavivirus	Dengue virus	*Ae. aegypti* *Ae. albopictus*	Increased risk of DHF and DHS[54] Increased pre-eclampsia, obstetric haemorrhage, miscarriage, pre-term delivery[55–57]	1.6% transmission in cohort of 65[64] One prospective study reports 18.5–22.7%[65]	CYD-DTV vaccine[53]	Supportive, monitor for need of C-section
Zika	flavivirus	Zika virus	*Ae. aegypti*	IUGR, oligohydramnios, stillbirth, miscarriage[72]	CZS (microcephaly, ventriculomegaly)[11]	2 vaccines in phase II trials (VRC 705, mRNA 1325)[75]	Supportive
Japanese encephalitis	flavivirus	Japanese encephalitis	*Culux*	Miscarriage, stillbirth. Outcomes similar in 3T infections compared with background population.[79]	Virus identified in brain and liver of stillborn[79]	Vaccine available IXIARO®, live attenuated vaccine[80,81] not approved in pregnancy	Supportive
Chikungunya	togavirus	Chikungunya virus	*Ae. Albopictus*	Increased rate of admission[84] Sepsis syndrome in mother[17]	Occurs in antepartum period, 50% of newborns develop severe complications[12,17]	Standard protective measures	Supportive
Tick borne							
Lyme disease	spirochete bacterium	*B. burgdorferi s.l. complex* (*incl afzelii, garinii, miyamoti*)	*I. scapilaris* *I. ricinus* *I. pacificus* *I. persulcatus*	Stillbirth[102] Possible congenital malformation including cardiac[98]	Spirochetemia of newborn,[91–93] ECM rash[96]	Standard protective measures	Doxycycline contraindicated Amoxicillin 500 mg TID x14–21 days[105] Ceftriaxone 2 g OD[104–106]

(Continued)

Table 1. (Continued)

Infectious disease		Organism	Vector	Complications in pregnancy	Vertical transmission	Prophylaxis/ vaccination	Treatment in pregnancy
Human Granulocytic Anaplasmosis	gram negative bacterium	*Anaplasma phagocyto-philum*	*I. scapilaris* *I. pacificus*	Mild symptomatic course in pregnancy.[115] Miscarriage has been described[113]	Case reports of vertical transmission. No vertical transmission seen in treated mothers[114,115]	Standard protective measures	Doxycycline contraindicated (but has been used in some cases) Rifampicin 10 mg/kg bd × 5–7 days[110,111] Penicillin if LD coinfection suspected
Human Monocytic Ehrlichiosis	gram negative bacterium	*Ehrlichia chaffensis*	Lone star tick Amblyomma (dog tick)	Minimal data. One case of a mother who developed appendicitis and had good outcome for mother and baby[116]	No data	Standard protective measures	Doxycycline used in one case with good outcome[7] Rifampicin 10 mg/kg bd × 5–7 days[110,111]
Babesiosis	protozoa	*Babesia microti* *Babesia divergens*	*I. scapilaris* *I. pacificus* *I. ricinus*	Severe infection mimicking HELLP syndrome seen in pregnancy[14]	Rare, congenital syndrome of fever, thrombocytopenia, anaemia[124]	Standard protective measures	Clindamycin 600 mg PO TID + quinine 650 mg PO TID × 7–10 days (better placental penetration than standard atovaquone and azithromycin)[14]
Tick-borne encephalitis	flavivirus	Tick-borne encephalitis	*I persulcatus* *I ricinus*	Limited data, self-limiting illness, no evidence of adverse events in pregnancy	No evidence of vertical transmission in a single case of infection in pregnancy[130]	Standard protective measures	Inactivated vaccine available risk/benefit analysis for use in pregnancy[131]
Relapsing Fever	spirochete bacteria	*B. miyamoti (seven other species)* *B. recurrentis*	Ornithodoros (soft shell ticks) Ixodids lice	Decreased birth weight, pre-term delivery, miscarriage[134,135]	Transmission in utero and during pregnancy[136,138]	Standard protective measures	Doxycycline contraindicated Erythromycin[139] - 7–10 days TBRF - single dose LBRF
Rickettsial diseases							
Rocky Mountain Spotted Fever	proteo-bacterium	*Rickettsia rickettseii*	(Hardshell tick) *Dermacentor variabilis* *Dermacentor andersoni*	Adverse outcomes in pregnancy. Case series of 10 pregnancies, 3 maternal deaths, 3 miscarriages, 3 neonatal deaths[144]	No evidence of vertical transmission	Standard protective measures	Chloramphenicol 50–75 mg/kg in 4 divided doses for 5–7 days or until afebrile for 48–72 h. Doxycycline IV in severe cases[143]
ET	proteo-bacterium	*Rickettsia prowazekii*	(Human louse) *Pediculosis humanus*	No evidence for increased complication rate in pregnancy	No evidence of vertical transmission	Sanitation/ hygiene	

(Continued)

Table 1. (Continued)

Infectious disease		Organism	Vector	Complications in pregnancy	Vertical transmission	Prophylaxis/ vaccination	Treatment in pregnancy
ST	proteo-bacterium	*Orientalis tsutsugamushi*	(Mite) *Leptotrombidium*	High levels of adverse outcomes in all trimesters including miscarriage, maternal death in some cases in studies of both ST and MT[151,152]	No evidence of vertical transmission	Standard protective measures	Doxycycline, azithromycin, rifampicin[155]
MT	proteo-bacterium	*Rickettsia typhi*	(Rat flea) *Xenopsylla cheopis*		No evidence of vertical transmission	Standard protective measures	Doxycycline[153] (azithromycin inferior)
Fly borne diseases							
Chagas disease	protozoa	*Trypanosoma cruzii*	(reduviid bug) *Triatima infestans Rhodnius prolixans*	Maternal infection does not appear to have negative outcomes during pregnancy or delivery[161]	Congenital CD in 5% of cases. Associated with prematurity, low birth weight, hepatosplenomegaly, anaemia, thrombocytopenia[161]	Standard protective measures	Treatment of mothers not advised during pregnancy[163] Benznidazole and nifurtimox in newborn children min. 60 days of therapy[164]
Leish-maniasis	protozoa	*Leishmania*: *infantum donovani aethiopica*	(sandfly) New world: *Lutzomyia* Old world: *Phlebotomus*	Hepatosplenomegaly in pregnancy can be occult due to the increasing size of the uterus	A systematic review of 17 vertical transmissions showed 27% neonatal mortality[169]	Standard protective measures	Liposomal Amphotericin B safe but difficult to procure in resource limited settings. Miltefosine and pentavalent antimony are not advised in pregnancy due to teratogenicity and lack of data respectively
Bartonellosis (Carrion's disease)	proteo-bacterium	*Bartonella bacilliformis*	(sandfly) *Lutzomyia verrucarum*	Carrion's disease is associated with high maternal mortality, miscarriage, preterm birth and foetal death[174]	Vertical transmission is described in case reports[175]	Standard protective measures	Chloramphenicol is the mainstay of treatment, ciprofloxacin, rifampicin and streptomycin have also been used. No data exists on treatment of pregnant[173]

ET, epidemic typhus; HELLP, haemolytic anaemia, low platelets, elevated liver enzymes; IUGR, intrauterine growth restriction; LBRF, louse-borne relapsing fever; LD, Lyme disease; MT, murine typhus, ST, scrub typhus; TBRF, tick-borne relapsing fever.

In endemic areas, 125 million pregnant women are at risk of acquiring malaria[24]; 25 million pregnant women in SSA are at risk yearly, 25% of whom have signs of placental infection at delivery.[25] *Plasmodium falciparum* is the most burdensome, affecting primarily SSA. *Plasmodium vivax* is rarer in SSA but has a much broader distribution globally, including temperate climates in SEA and the western pacific region.[26] Although not considered as virulent as *falciparum* malaria, *P. vivax* carries a significant burden of the global impact of malaria[27,28] Fevers are not always a feature of malaria in pregnancy and infections can go unchecked for prolonged periods. A spectrum of severity exists for pregnant patients presenting with malaria dependent on geographical endemicity, gravid status, and country of origin of the mother. In low endemic areas with primigravid mothers with reduced prior exposure, malaria tends to present as acute febrile illness with higher risk of severe malaria and death.[29] These women are at higher risk for complications as they lack pre-existing protective antibodies. Highly endemic areas where there is a higher probability of recurrent infections confer partial immunity against malaria.[30] Multigravida women tend to present in this manner, and, for this reason, pregnant women are a significant reservoir of the disease. *P. falciparum* is the causative organism in over 90% of cases, with *P. vivax* the second most common cause. Complications of malaria include anaemia, haemolysis and acute respiratory distress, and these complications are seen more frequently in women who are pregnant, particularly in the second and third trimesters.[31] This increased risk of more severe disease persists for up to 2 months post-partum.

Treatment limitations are an issue in pregnancy. Chloroquine, previously the mainstay of treatment in pregnancy, is ineffective in areas endemic for *P. falciparum*. Primaquine, the recommended treatment of *P. vivax* and *P. ovale* hypnozoites and a preventative agent of recurrence of these diseases, is contraindicated due to risk of glucose-6-phosphate dehydrogenase (G6PD) deficiency and risk of haemolytic anaemia. Prophylaxis with tetracyclines, primarily doxycycline, is also contraindicated. Artemesinin-based treatment (ACT) is now the standard of care in SSA, but it is not indicated in the first trimester due to safety concerns. Current WHO recommendations for confirmed infection advise primaquine and clindamycin for first trimester and ACTs in second and third trimester. High cure rates have been seen in pregnancy with these combinations.[32] The current global treatment strategy in pregnancy is 'intermittent prevention and treatment in pregnancy' (IPTp) with three temporally spaced doses of sulfadoxine-pyrimethamine. The first dose is given in the second trimester, with 1 month between subsequent doses thereafter at antenatal clinic visits. To date, 39 African countries have adopted the policy. This strategy has reduced the incidence of low birth weight, maternal anaemia and perinatal mortality. This strategy does not affect gameocytemia, which can be as high as 5% in endemic areas and persists despite IPTp in pregnant women.[33]

In addition, the use of insecticide treated mosquito nets (ITNs) in pregnancy has increased from 24% in 2010 to 61% in 2017.

Vaccination for *P. falciparum* malaria commenced in both Malawi and Ghana in April 2019 and subsequently in Ghana in September 2019 with a novel vaccine RTS,S. A potential target for malaria in pregnancy is the VAR2CSA protein that is up-regulated on surfaces on placentally sequestered parasites. This large protein has multiple binding domains, and studies have shown that pregnancy outcomes in relation to antibody levels against VAR2CSA are variable.[25] All patients had an immunological response to the vaccine. Only three, possibly related, grade 3 adverse events were seen.[34]

Mosquito-borne flavivruses

Arboviruses that cause vector-borne infections in pregnancy, primarily flaviviruses, include Dengue, Zika, WNV, chikungunya, Yellow fever and Japanese encephalitis. All are spread by aedes mosquitos and have variable distribution internationally. WNV is the most widely distributed. Endemic to North Africa, this virus has spread across North America, Asia and Europe. Most patients who acquire WNV are asymptomatic, 20–40% have mild, self-limiting symptoms of fever, joint pain, rash and lymphadenopathy. A small proportion (<1%) of patients with WNV will progresses to serious neurological meningitis, encephalitis and flaccid paralysis.[35] Pregnant women do not appear to have increased risk of adverse pregnancy outcome and, with available

data, foetuses do not appear to be more at risk of neuro-invasive disease, although more studies are needed.[36] Yellow fever is another flavivirus with self-limiting illness and generally with good outcomes, and is the only flavivirus with confirmed transmission through breast milk, although dengue, zika and WNV have all been detected.[37] Although flaviviruses have huge clinical implications, there is no targeted anti-viral therapy for them. Dengue, Zika, and Japanese encephalitis have more serious implications in pregnancy and will be discussed further.

Dengue

One study estimated that 390 million individuals are infected with dengue yearly, 96 million of whom develop symptoms.[38] Endemic areas are primarily tropical and subtropical; Latin America, Asia, and SSA. The primary vector is the *Ae. aegypti* mosquito and, to a lesser extent, *Ae. albopictus*.[39] Four serotypes of the flavivirus exist, and infection with one type confers lifelong immunity to that specific type, and partial and temporary immunity to the others. Hyperendemic areas can harbour multiple serotypes. Patients with mild disease can experience flu-like symptoms, fevers, joint pain, myalgia and cough within 1 week of infection. The commonality of these symptoms amongst other vector-borne disease like malaria, chikungunya and yellow fever, also endemic to areas with dengue, can make these diseases difficult to differentiate. Furthermore, some patients ($<5\%$) can develop more severe variants of the disease, with Dengue haemorragic fever (DHF) characterised by low platelets with petechiae, bleeding, injected conjunctivae, abdominal pain and capillary leak syndromes with pleural effusions and third spacing of fluid in other areas. A more serious phenotype of the disease called Dengue shock syndrome (DSS) requires urgent medical supportive measures and has a high mortality rate.[40] Clinical features at presentation cannot accurately predict which patients will progress to severe disease. A systematic review of predictive tools found some have accuracy as high as 86% when applied to infection with symptom onset within 3 days and 98% for prediction of 30-day mortality.[41]

Virus isolation using mammalian/mosquito cell lines or live mosquitos are definitive but labour intensive and time inefficient, and have largely been replaced by quicker, less expensive tests.[42] These novel investigations, like enzyme-linked immunosorbent assay (ELISA) against NS-1 antigen, real-time polymerase chain reaction (RT-PCR) and serology must be performed and interpreted in the context of clinical presentation, duration of symptoms, history of previous dengue infection and vaccination. NS-1 antigen is a useful marker as it can be detected throughout infection and the subsequent period prior to antibody formation.[42] The test can be used as a predictor of severity if $\geqslant$600 ng/ml within the first 72 h in laboratory assays, and, more practically, with persistence of positivity for five or more days using commercially available kits.[43,44] RT-PCR, also referred to as nucleic acid amplification testing (NAAT), has a rapid turn-around time, is a sensitive and specific test and is generally positive from the time of onset of symptoms.[45] Standardised commercial kits can be expensive and many laboratories, especially in resource-limited settings, use non standardised in-house testing with variable sensitivity. RT-PCR has a narrow window of positivity, which limits its value. Serology, as in nearly all diagnostic scenarios, is less sensitive in early infection than other modalities like PCR. Interestingly, with dengue infection, IgM can be positive as early as day 3 and can remain positive, as with many flavivirus infections, for many months, which can make it difficult to determine acute infection during pregnancy.[46,47] Plaque reduction neutralization tests (PRNT) are quantitative and specific tests for flaviviruses using identification of neutralizing antibodies (nAbs), primarily IgG. A $\geqslant$4-fold increase in titre of specific nAbs for a flavivirus infection compared with other flavivirus nAbs that may be tested indicate the specific cause of infection.[48]

Difficulties with diagnostics arise with recurrent infection, with infection post-vaccination and infection in areas endemic for both dengue and zika viruses. An amnestic immunological response can be seen with acute infection when individuals have antibodies because of previous infection or vaccination; this can significantly reduce NS-1 antigen and IgM response and rapidly increase IgG neutralizing antibody response, potentially precluding identification of the specific flavivirus. IgM and IgG can also be falsely positive when testing for one virus in the presence of the other due to similar viral surface epitopes, which creates difficulties elucidating single *versus* dual

infection.[49] Many commercial serological kits are available for dengue and some combine NS-1 ELISA to confer very high levels of detection of acute infection,[50] the high specificity of NS-1 ELISA for dengue virus is also highly advantageous in identifying true dengue infection.[51]

Current Centers for Disease Control and Prevention (CDC) recommendations for symptomatic pregnant patients with suspected zika/dengue infection include collecting serum and urine samples within 12 weeks of onset of symptoms to test nucleic acid amplification test (NAAT) and IgM for dengue/zika. If NAAT is negative with a positive IgM, PRNT should then be done with nAbs directed against all endemic flaviviruses in that region to aid in differentiating the true cause of infection.[52]

Previous infection and, in particular, infection post-vaccination can result in the development of DHF. Use of the live attenuated vaccine CYD-TDV has been adopted in more than 20 endemic countries. Data for use of the vaccine is limited. Inadvertent pregnancy in those exposed to the vaccine in CYD-TDV trials show no significant differences in pregnancy outcomes compared with pregnancies in placebo trial-arms although numbers were limited.[53] The WHO has released a position statement advising screening, and administering the vaccine only to those with previous evidence of infection. Mortality can be as high as 20% for severe disease but can be reduced to $<1\%$ with supportive medical care, in particular appropriate hydration, as at present no targeted viral therapy exists.

Dengue in pregnant women appears to be more severe when compared with the general population. Pregnant women have both increased severity of disease and increased mortality. The risk of developing DHF/DSS was increased 3.4 times in pregnancy in one study, increased with progression of pregnancy and is most common in the third trimester.[54] Overall mortality in the same study was 7.4%. A cohort analysis in Brazil found dengue increases maternal mortality 3-fold while DHF increases mortality 450-fold.[16] Complications unique to pregnancy, such as increased risk of pre-eclampsia and obstetric haemorrhage, have been reported. In one study of 82 clinical and laboratory confirmed dengue infections, 15.9% developed severe dengue infection. Of those, 38.5% of deliveries were emergency caesarean section (C-section) due to foetal distress, 30.8% developed obstetric haemorrhage, 15.4% developed pre-eclampsia and 7.7% developed eclampsia. In non-severe symptomatic dengue, no increase incidence of described complications was seen.[55] One small study of 15 patients in India with confirmed dengue showed pregnancy-induced hypertension and DHF occurred in 25% of patients, and nearly 80% of patients also developed thrombocytopenia.[56]

Despite the high incidence of dengue internationally, data for foetal outcomes are poor. Most studies are case series with conflicting results; a meta-analysis did show increased odds [odds ratio (OR) 3.51] of miscarriage for dengue during pregnancy.[57] The largest study is a cohort of routine clinical data between 2006 and 2012 in Brazil, capturing over 16.7 million live births, of which 17,673 (0.1%) had a linked dengue notification within 9 months prior to birth. Results show dengue infection was associated with slightly increased risk of pre-term birth (7.3% *versus* 7.9%) and low birth weight (7.2% *versus* 8.4%) but no difference was seen with size for gestational age. Risk increases with haemorrhagic fever (OR 2.4 preterm birth and OR 2.1 low birth weight).[58] The same research group used population data to identify risk of stillbirth and found the odds were 0.2% in those with reported dengue *versus* 0.1% for background populations. This risk increases 5-fold for women with severe dengue.[59] Another study from Brazil retrospectively reviewed data from 3898 pregnant women with symptomatic dengue and also found increased odds of preterm delivery. No increase in congenital malformations or low birth weight was seen.[60] The effects of dengue in pregnancy likely reflect the effects on the mother rather than the foetus given gestational age is not affected. Although small studies have shown immune-histological changes consistent with viral damage do occur in the placenta including hypoxia, deciduitis, intervillitis and the presence of viral antigens.[61]

Maternal-to-foetus antibody transfer was seen at 99.3% in a study of 505 pregnant dengue-infected women, in the half that had developed antibodies.[62] Although this may be an effective protective mechanism in utero, this may lead to severe dengue in early childhood in those who acquire primary infection.[63] Cases of vertical transmission of

dengue have occurred in a cohort of 65 women, IgM specific antibody was seen in one paired cord blood sample indicating a 1.6% transmission rate.[64] Most cases of vertical transmission likely occur at delivery and are likely dependent on a high viral load at that time. A prospective study of 53 pregnancies during the French Guiana epidemic in 2012–2013 estimated a significantly higher rate of mother to child transmission of between 18.5% and 22.7% depending on the calculation method used. They also found transmission did occur in early pregnancies.[65]

As for the general population, treatment of dengue is supportive; pregnant patients should have close monitoring should the need for emergency C-section arise. Global strategies to reduce transmission besides vaccination are similar to targeted prevention of other vector-borne diseases like malaria.

Zika virus

Similar to dengue, zika is a flavivirus that affects tropical areas and is found primarily in Latin America, with new cases arising in the southern states of North America. Its spread is facilitated by the genus *Aedes*, primarily *Ae. aegytpi*, and mechanisms underlying its spread are likely similar to those increasing spread of other vector-borne diseases. It can also be spread through sexual contact, blood transfusion and organ transplantation.[66] It was first identified in humans in 1952 in Uganda and the Republic of Tanzania with the first outbreaks in 2007 in Yap, Micronesia, 2013 in French Polynesia and 2015 in Brazil.[67]

As described, there is potential for cross reactivity, as some endemic areas like South America and Asia have over 75% serological positivity for dengue.[68] Similar issues arise with PCR testing as viraemia peaks for 1 day and can frequently be undetectable by day 3. Interestingly, viraemia can persist in pregnancy for many weeks, rendering PCR testing particularly useful in this setting.[69] Unlike persistence of positivity of NS-1 antigen in dengue, persistence of PCR positivity in zika virus does not reflect or predict disease severity or progression. A number of hypotheses have been proposed for this phenomenon, including placental trophoblasts acting as a reservoir for zika, spill over from viral replication within the foetal neurological reservoir, and delayed immune clearance in pregnancy.[69]

As with dengue most patients are asymptomatic during infection, some may develop mild viral symptoms like rash, myalgia, arthralgia, headache, nausea, conjunctivitis. The most serious difference between dengue and zika virus that arises in pregnancy is the transplacental movement of Zika and its neurotropism for the developing neurological system in the foetus, which can result in severe congenital abnormalities.[70] Other unique features of Zika are its ability to trigger post-viral immune-mediated phenomena like Guillan-Barré syndrome, neuropathy and myelitis.[71]

Primary infection in pregnant women does not appear to be increased in endemic areas. A meta-analysis suggests rash is the most common symptom, with fevers, chills, malaise, myalgia and arthralgia amongst others also feature. Out of 18 studies, 12 suggested most symptoms occur in the first trimester; 7 studies were performed in asymptomatic patients. One observational study suggests lymphadenopathy occurs more frequently in pregnancy.[72]

Neurological complications do not seem to be more common in pregnancy. Emergency C-section, intra-uterine growth restriction due to placental insufficiency, and oligohydramnios have been seen. Miscarriages and stillbirth have also been reported.[72]

Of women with Zika in the first trimester, 15% went on to deliver neonates with Zika-associated birth defects. This percentage reduces to 5% and 4% in second and third trimesters in pregnancy.[73,74] No statistically significant difference is seen in those patients with symptomatic *versus* asymptomatic infection. Congenital Zika syndrome (CZS) presents a host of neurological abnormalities, including microcephaly, ventriculomegaly calcifications and anomalies of corpus callosum, amongst others, and can occur in 33–100% of infants. Clinically, 70–100% of children have motor abnormalities, with other issues including epilepsy and a range of neurological issues.[11]

As with other flaviviruses, no directed treatments currently exist for zika virus. At present, two vaccines have reached phase II clinical trials, VRC 705 (a DNA vaccine) and mRNA 1325 (an mRNA vaccine).[75] Due to significantly reduced incidence of the virus, performing meaningful, well-powered

clinical randomized controlled trials with defined efficacy endpoints is difficult. Identifying immunological markers that are associated with conferred vaccine efficacy may be useful.[76]

Regarding prevention in pregnancy, the CDC recommend avoidance of travel to areas of zika outbreak and, if travel is necessary, to employ basic prevention strategies like using Environmental Protection Agency (EPA) approved insect repellent, mosquito nets and staying in air-conditioned accommodation with window and door screens. Use of condoms for the duration of the pregnancy for partners who have been to endemic areas is also advised. Testing for zika should be done in symptomatic women or those with identified foetal abnormalities on ultrasound who have travelled to an endemic area. For those living in endemic areas, symptoms alone warrant testing.[77]

Japanese encephalitis

Japanese encephalitis virus (JEV) is a *Culex* mosquito-borne flavivirus that has a spectrum of severity from no symptoms to fever, headache, rhinorrhoea, convulsion, coma, flaccid paralysis and encephalitis. Endemic to South/SEA, JEV is a virus of birds and pigs with humans an incidental end host. Approximately one-third of patients admitted to hospital with the disease die, and half of survivors have significant neurological sequelae.[78] Data in pregnancy is limited, adverse outcomes, including abortion, have been seen, although infections in third trimester do not appear to increased adverse outcome compared with non-infected women. Vertical transmission has been seen in cases of stillbirths, with presence of the virus in brain, liver and placental tissue.[79] At present, vaccines are available but not approved in pregnancy due to lack of data, and currently carry a United States Food and Drug Administration (FDA) C rating. A live attenuated vaccine is currently in use in China and other countries in SEA. IXIARO® – an inactivated VERO cell cultured JEV vaccine – is now immunogenic and safe in children >2 months old and should be considered in those, including women of childbearing age, travelling to endemic areas.[80,81]

Togaviruses: Chikungunya

Chikungunya virus (CHIKV) is a non-flavivirid mosquito-borne infection that causes significant morbidity and, on occasion, mortality. CHIKV is a *Togavirus* first described in the 1950s that has spread from Africa to the Indian Ocean and Asia. Mutations that confer its ability to spread *via* the mosquito *Ae. albopitcus* have hugely increased its virulence, cause devastating outbreaks in the Indian Ocean and sparking scientific interest in the vector-borne infection.[82] The disease is biphasic, with an acute viral phase featuring fevers, headache, myalgia, fatigue, and maculo-papular rash and arthralgia, with onset of symptoms up to 7 days post-inoculation. Gastrointestinal illness, including nausea, vomiting and diarrhoea is debilitating and can occur in up to 47% of cases. The second stage is a persistent arthralgia, and many patients fulfil criteria for rheumatoid arthritis (RA); this can persist for months.[82] As with other flaviviruses, diagnosis is made with RT-PCR and serology. A number of commercially available PCR and IgM ELISA tests are available.[83]

The outbreak on Réunion Island in 2005–2006 showed that CHIKV can be spread vertically in pregnancy. Robust prospective studies show the peri-partum period is the most likely time of infection in newborns, with symptoms beginning in the hours post-delivery. Over a 22-month period, Gérardin *et al.* showed that 749 antepartum or intrapartum infections in pregnant women with confirmed infection by PCR or serology resulted in foetal infection nearly exclusively in near-term deliveries in mothers who were viraemic at that time. Of 39 mothers with viraemia, 19 (48.7%) resulted in neonatal infection. No neonates had detectable virus or symptoms on day 1 post-partum. Pain, joint oedema, thrombocytopenia, rash and deranged liver blood tests were common features. A majority (52.6%) of neonates progressed to severe disease with one or more features of haemorrhagic fever, disseminated intravascular coagulation (DIC), haematemesis, shock, mechanical ventilation, need for vasopressors and encephalopathic features, including intracerebral bleeds and parenchymal petechiae. Rarity of placental histological lesions seen in these pregnancies and absence of RT-PCR-positive results in the breastmilk of 20/33 viraemic mothers are in keeping with vertical transmission in the intra-partum period.[17] A prospective study during the same outbreak in women infected during pregnancy with CHIKV ($n = 658$) and non-infected women ($n = 628$) showed no significant difference in adverse events

of preterm delivery, low-birth weight, preterm delivery, miscarriage, stillbirth or admission to neonatal care, but did show increased risk of hospitalisation (40% *versus* 29%). It must be noted that the majority of CHIKV infections 486 (74%) were in the first and second trimester. Only four (0.6%) of the study patients were symptomatic and positive in the 7 days before delivery, and one neonate was infected with CHIKV.[84] In essence, these studies of the Réunion Island outbreak indicate that the risk of complications in the neonate is related directly to novel vertical infection in the antepartum period, and that mothers are generally mildly affected by the virus. This narrative has changed in recent times, with emerging infection in South America. In 60 hospitalised pregnant women in Colombia with chikungunya, 9 were admitted to the Intensive Care Unit with septic shock and organ dysfunction; none died. Of 15 symptomatic mothers at the time of delivery, no newborns developed symptoms of chikungunya; 50% of babies of viraemic mothers were tested with RT-PCR and all were negative.[85] A systematic review of mother to child transmission of CHIKV found an overall rate pooled rate of 15.3% of symptomatology in newborns to mothers diagnosed with CHIKV infection during pregnancy; this increased to 50% among intrapartum maternal infections. The antepartum foetal death rate was 1.7% and a staggering 50% of children with symptoms at birth went on to develop long-term neurodevelopmental delays.[12] There are several promising vaccines in development and potential candidates for antiviral directed therapy, but none are fully developed at present.[86]

Tick-borne infections in pregnancy

Hard-shell tick-borne infections affect primarily northern hemisphere temperate climates but have been found on all continents including Australia. One of the biggest differences between tick-borne infections and mosquito-borne infections is the lifecycle of pathogens. Humans tend to be 'accidental' end hosts for zoonoses that have life cycles in ecosystems with multiple animal hosts as is the case with tick borne infections, whereas humans are central to the life-cycle of mosquito borne diseases like malaria. With rising global temperatures, diseases like Lyme borreliosis are also rising in incidence in Europe and North America, as ticks have a longer feeding season.[87]

Lyme disease

Lyme disease (LD) was first described in the town of its namesake in the State of Connecticut (Old Lyme), when a case series of children were misdiagnosed as having juvenile arthritis and were in fact found to have spirochetal illness in 1977.[88] The causative organism was identified as *Borrelia burgdorferi*, whose name is also now also used to describe a larger Lyme borreliosis complex (*Borrelia burgdorferi sensu lato*), which includes *Borrelia burgdorferi sensu stricto, borrelia garinii, afzelii* and *miyamoti*, amongst others. Hard-shelled ticks *Ixodes scapularis* and *Ixodes pacificus* in North America, *Ixodes ricinus* in Europe and *Ixodes persulcatus* in Asia are the main vectors of the disease. Co-infection can occur with ehrlichia and babesia, as hard-shell ticks also harbour these infections. Within the tick life cycle, nymphal ticks are the most transmissible to humans, their primary hosts are small birds and rodents. The incidence of infection is dependent on climate and tends to be more common in countries with high levels of forestation.

The most common symptoms of early Lyme infection is a bull's eye rash radiating from the bite, erythema migrans (ECM), in association with fever, headache, meningitis, radiculopathy and arthritis. Later presentations feature recurrent arthritis, carditis, cranial nerve palsies, neurological issues like encephalitis, and myelitis.[89] A two-tier antibody testing algorithm is currently the international standard for testing. Initial testing is performed by enzyme-linked immunosorbent assay (ELISA); if positive, more specific second-tier Western blot testing is performed looking for five or more IgG bands or two or more IgM bands.[90] However, not all patients have positive tests, especially early in infection, in the setting of partial treatment with antibiotics, and in immunocompromised patients.

Vertical transmission of LD was first suspected in 1983 in a newborn with hyperbilirubinemia and spirochetes on a blood film. The mother described arthritic symptoms but no LD or syphilis serology was performed in this case.[91] In 1985, a 28-year-old mother who acquired LD in the first trimester, with classic ECM rash, delivered at 35 weeks. The child died of congenital heart disease and autopsy showed spirochetes infiltrating the spleen, kidneys and bone marrow,

but not cardiac tissue. Post-delivery, the mother's Lyme immunofluorescence assay (IFA) was positive 1:128.[92] *Borrelia burgdorferi* was identified in the myocardium using an immunohistochemical technique.[93]

A number of case reports in subsequent years present compelling immunohistological evidence of spirochetaemia in stillbirths in mothers with clinical and/or laboratory confirmed LD.[93,94] Other evidence for possible transplacental transmission comes from mothers found to have antibodies against Borrelia; of 60 patients, 5% had evidence of spirochetes in placenta tissue using silver stain. Two of three were PCR positive for *B. burgdorferi* in one study.[95]

A 3-week-old who developed a classic ECM skin rash post-partum was found to have *B. burgdorferi* isolated from skin specimens, indicating the possibility of vertical transmission.[96] Case reviews of 19 women with LD in pregnancy reported adverse events in five cases of foetuses, which suggested the possibility of congenital LD.[97]

Robust epidemiological studies of LD in pregnancy are lacking at present and best evidence is dependent on small under-powered studies. The largest study comes from hospitals in upstate New York in an area that was highly endemic between 1988 and 1990.[98] Of 2014 women identified, 11 (0.7%) were found to be seropositive at their first prenatal visit, 5 of whom had LD in the past. These 5 patients also represented 7.7% of the total of 65 patients who report LD in their past; the remaining 60 were seronegative. One patient seroconverted from the prenatal visit to postnatal, cord blood also showed LD IgG confirmed with Western blot, no adverse effects were seen in the child up to 1 year. Of 10 of the 11 seropositive women, 3 had congenital anomalies, compared with 175 of 1058 seronegative and clinically negative patients. Clinical LD in a patient's past was not associated with adverse outcomes including miscarriage or foetal death. Overall foetal death was not associated with any index of LD exposure. They did find a significant association between cardiac defects and areas of high endemicity of LD, past miscarriage with a history of tick bite, and having had a tick bite within 3 years of birth and congenital defects. The study does not comment on treatment of LD in those with clinical LD or antibody positivity, and the study was too small to infer any potential risks of congenital malformation in women with seropositivity.

Summaries warning of the risk of transplacental transmission of *B. burgdorferi* and possible adverse outcomes have been documented by the CDC,[99] WHO,[100] Canadian Public Health authorities and the National Institutes of Health.[101] The March of Dimes highlights possible adverse outcomes in pregnancy, including certain birth defects and stillbirth, if mothers are untreated for LD.[102]

A systematic review of gestational LD examining cases and epidemiological studies identified 59 cases between 1969 and 2017. There was significant variability in the extent of diagnostics performed in these cases. One case described complete features of clinical and laboratory results consistent with vertical transmission of *B. burgdorferi*.[103] A negative outcome for the foetus or newborn occurred in 36 (61%) of cases, 12 cases report miscarriage or foetal death, 8 report newborn death and 16 report other abnormalities post-delivery, including syndactyly, respiratory distress and hyperbilirubinaemia. Of 23 healthy newborns, information on treatment was available in 19, 18 (95%) of whom were treated during pregnancy. In cases with negative outcomes, and where data were available, 41% (14/34) of patients received LD treatment during pregnancy. Despite this apparent high level of adverse outcomes associated with LD in pregnancy and the trend towards better outcome with treatment, the authors found that epidemiological studies did not find increase adverse events in LD pregnancies. Many studies compare pregnant women in endemic areas with features or serology of LD with non-LD and are underpowered. One of the difficulties is elucidating the true adverse effects of gestational LD by identifying mothers who had active untreated infection during pregnancy. The review identifies four studies comparing treated and untreated mothers with LD. The largest study of 96 confirmed cases shows that untreated women have a significantly higher risk of adverse outcome (OR 7.61, $p < 0.0004$), and that intravenous treatment may be more efficacious than oral, with adverse outcomes in 12% of parentally treated, 31.6% of orally treated and 60% of untreated women with LD during pregnancy.[104] A trend towards better outcome with treatment was seen in the other three smaller studies that

did not reach significance. Overall, the review found decreased adverse events with treatment when performing a random effects meta-analysis of 10 studies with data available on treatment, 11% *versus* 50%.[103]

The literature on LD in pregnancy is, at present, incomplete due to lack of intensive investigations, and lack of longitudinal follow up of exposed infants. As we have seen with another spirochete, syphilis, it is plausible that congenital infection occurs with LD. Whether a congenital syndrome occurs as a result of this in utero infection remains to be further investigated.

Treatment of LD in pregnancy is more complicated due to the contraindication of doxycycline. Second-line treatment with amoxicillin is advised, and recommendations suggest the same treatment duration as for non-pregnant infection.[105] Some clinicians report preferential use of intravenous (IV) ceftriaxone 2G daily for 14 days for pregnant women with ECM, reporting a positive outcome in pregnant women and also good pregnancy outcomes.[104,106,107]

Ehrlichiosis

Ehrlichiosis, caused by *Anaplasma phagocytophilum* and *Ehrlichia chaffensis* are gram negative obligate intracellular organisms spread by the hard-shelled ticks *I. scapularis* and Lone Star tick (*Amblyomma americanum*), respectively, found in North America. These genetically distinct but linked organisms also share a common ancestor with other obligate anaerobes like *Wolbachia* and Rickettsiae.[108] *A. phagocytophilum* causes human granulocytic anaplasmosis (HGA) and *E. chaffensis* causes human monocytic ehrlichiosis (HME). Both diseases have similar presentations of febrile illness.

Infection with these pathogens is seen post outdoor activity and is clinically characterised by flu-like illness, fever, headache, myalgia and arthralgia. Rash and neurological features like meningitis and meningoencephalitis point towards HME. Laboratory abnormalities of leukopenia, thrombocytopenia, transaminitis, raised alkaline phosphatase and lactate dehydrogenase (LDH) are a feature of these diseases. HME is a more severe disease process, can present as single or multi-organ failure, is associated with septic shock and carries a higher mortality, particularly in the immunocompromised.[109] Morulae and intracellular inclusions are characteristically seen using Wright or Giemsa stain in neutrophils in HGA and monocytes with HME. The presence of these phenomena can be as low as 1–20% in the latter. For HGA, IFA with 4-fold increase in antibodies is the diagnostic test of choice but peripheral smear and serum PCR can be more sensitive in early disease, performed before initiation of antibiotics. Immunofluorescence (IF) is unreliable as a diagnostic tool in HME. In pregnancy, rifampicin 10 mg/kg bd (max dose 600 mg bd) is recommended for 5–7 days, although data for this is limited and comes from individual case reports and *in vitro* sensitivities.[110,111] Doxycycline has been used occasionally in pregnancy for this reason despite generally being contraindicated. Penicillin-based antibiotics should also be added if LD is considered a possibility. Although poorly described in pregnancy, some case reports have shown that HGA can be treated successfully[112]; cases of miscarriage have been reported in patients treated for HGA with doxycycline.[113] Vertical transmission has been reported in one mother who had tick exposure 1 week prior to delivery,[114] another case series also reports vertical transmission in one of six women but no cases were seen in individuals treated with either rifampicin or doxycycline. HGA appears to have a mild course in pregnancy with no major adverse outcomes seen.[115] In HME, only one adverse outcome has been reported in pregnancy; a mother developed appendicitis and was treated with doxycycline. Both mother and baby had good long-term outcomes.[116]

Babesia

Babesiosis, caused by *Babesia microti* in North America, is an intra-erythrocytic protozoal infection spread by Ixodes hard-shelled ticks. In Europe, *B. divergens* is the most common species. Infection is well described in animals but less so in humans compared with North America. Co-infection with other pathogens that also use *I. scapularis* as a vector, like *A. phagocytophilum* and LD, does occur. The degree of co-carriage of babesia and LD varies geographically and with the stage of development of ticks.[117] A seroprevalence study of babesia in proven LD using two-stage testing in New York indicated a 28.6% coinfection rate.[118] Babesia is also the most

common transfusion-related infection reported to the FDA.[119] Clinical characteristics include fever, malaise, chills, myalgia, night sweats, weight loss, organomegaly, mild-to-moderate haemolytic anaemia and thrombocytopenia.[120] A characteristic 'maltese cross' appearance of tetrads of merozoites can be seen within red blood cells on Wright giemsa stain. PCR, IFA tests and serology are also used in diagnosis.[121] Severe disease can be seen with heart failure, acute respiratory distress syndrome (ARDS), DIC, liver failure, renal failure and splenic rupture. Patients who have received blood transfusions from endemic areas, who present with acute symptoms or are severely unwell should be tested for babesiosis. Immunocompromised patients, particularly patients with B cell lymphoma, asplenia and treatment with rituximab, can experience persistence and relapse of infection and higher mortality.[122] Longer treatment durations are required in these patients.

As pregnancy is a relative immunocompromising state, severe babesia infections do occur in this setting. Babesia can mimic HELLP syndrome in pregnancy; complication and severity of disease do not correlate with the level of parasitaemia.[14] This may be due to complex host–pathogen interplay. Nine cases of congenital infection have been described in the literature, two of which were occult infections in mothers also infected with LD.[123] Infants with congenital infection display features of adult disease, such as fever, haemolytic anaemia and thrombocytopenia, and respond to transfusion and antimicrobial therapy.[124]

The first line treatment is atovaquone and azithromycin for mild–moderate disease and intravenous clindamycin and quinine for severe disease.[105] Clindamycin and primaquine are used in pregnancy as first line for mild and moderate disease also as they have better placental penetration and potentially could reduce transmission, although atovaquone and azithromycin have been used in pregnancy without complications.[14] The treatment duration is 7–10 days. Repurposed therapies like clofazimine and tafenoquine show promise for treatment of babesiosis in animal models. Unfortunately, as is the case with many drugs, insufficient data in pregnancy means these therapies are unlikely to be used in pregnancy in the near future.[125,126]

Tick-borne encephalitis

TBE is a neurotropic flavivirus that circulates in small mammal reservoirs as LD and similarly infects humans through hard-shell tick vectors in Continental Europe and Asia. Unique to its infectivity is the ability to spread by ingestion of contaminated raw milk.[127,128] Initially, infection is characterised by a transient phase of general malaise, fever, headache and myalgia for 5 days.[129] A second phase after 4–5 weeks is characterised by neurological sequelae; meningitis, meningoencephalitis, radiculitis, myelitis and paralysis. A case of infection in third trimester of pregnancy resulted in self-limiting illness with an uncomplicated spontaneous vaginal delivery. No TBE antibodies were detected in the healthy neonate.[130] No compelling cases of vertical transmission have been reported in the literature. An inactivated vaccine is available without data in pregnancy and should be used only when deemed necessary and appropriate risk/benefit ratio is assessed.[131]

Relapsing fever

Relapsing fever (RF) borreliosis is a significant cause of morbidity in temperate and tropical regions.[132] Both soft-shell (Ornithodoros) and hard-shell ixodid ticks are vectors for the disease. It must be noted also that 'louse-borne relapsing fever' (LBRF) is a more severe variant of the disease and tends to occur with poor living conditions and overcrowding; *Borrelia recurrentis* is the pathogen in this disease. Tick-borne relapsing fever (TBRF) is caused by a host of borrelia species; *B. hermsii, B. miyamoti, B. parkeri* and *B. duttoni* are some of the most common. The relapsing fever phenomenon is attributed to persistent change of the outer membrane lipoprotein. Few studies have been done on this group of bacteria, elucidating the interactions between host, tick and pathogens. LBRF can be severe, with shock, ARDS, multi-organ failure, Jarisch-Herxheimer (JH) reaction and opportunistic superimposed bacterial infections. Spontaneous abortion and mortality are high in pregnancy.[15] In pregnancy, relapsing fever borreliosis may cause up to 10–15% of neonatal deaths worldwide.[133]

A spectrum of severity is seen with TBRF in pregnancy, ranging from mild; with a slight decrease in birth weight and preterm delivery, to severe; with miscarriage, or neonatal death.[134,135] Case reports

have demonstrated a disparity between severity of disease in the mother and newborn. Symptoms of TBRF can be mild in pregnancy, with neonatal death as early as 30 h post-delivery.[136] Recent mouse studies have shown that TBRF can results in placental damage and inflammation, intrauterine growth restriction and foetal infection.[137] Case studies show transmission in utero and during delivery.[136,138] First line treatment of TBRF with doxycycline is contraindicated in pregnancy, and erythromycin is used. A 7–10 day course is recommended for TBRF and a single dose for LBRF.[139] A case of a patient 23 weeks pregnant with TBRF developed JH reaction post-treatment, went on to deliver a healthy term baby.[140]

Rickettsial disease

Rickettsiae are a group of intracellular coccobacillary proteobacteria that have a pan-global distribution and cause febrile illnesses of variable severity. They are spread through a number of vectors, including ticks, lice, fleas and mites. All rickettsial infections have a common ancestor. It must be noted that *Orientia tsutsugamushi* is a genetically distinct organism previously categorised as a rickettsia as it has similar clinical presentation, is a vector borne disease spread by mites, and causes scrub typhus (ST) in humans. There are over 20 species that can be broadly separated into four groups: ancestral, spotted fever, typhus and transitional.[141] The latter, primarily *R. prowazekii* is associated with epidemic outbreaks in large groups in close proximity due to the presence of the bacterium in human lice. Fever and rash are common features difficult to distinguish from other infections. A cutaneous eschar may be found at the site of inoculation by vectors. The presence of eschar is dependent on the rickettsial species causing infection; *R. rickettsii* and *R. coronii* have low-to-moderate probability of causing eschar, whereas its presence is pathognomonic of *R. africanum* and characteristically black in appearance. From a pathogenesis perspective, rickettsial diseases have a predilection for endothelial cells of the vasculature.[142]

Rickettsial infections are very sensitive to chloramphenicol and tetracycline antibiotics, both of which present problems in pregnancy. Publications of clinical outcomes in pregnancy are limited in general, as with other vector-borne infections, and appear to be worse than in the general population.

Rickettsia rickettseii

Rocky Mountain Spotted Fever (RMSF) is the disease caused by the most pathogenic rickettsial species: *Rickettsia rickettseii*. This febrile illness has mortality rates as high as 20–30% without treatment. Hard-shell ticks *Dermacentor variabilis* in central and eastern states and *Dermacentor andersoni* in the western United States are the most common vectors. This infection is also endemic to other western hemisphere countries: Canada, Colombia, Brazil, Argentina, Costa Rica, Panama and Mexico.[143] A classical triad of fever, headache and rash is present in 60–70% of patients by week 2 post-inoculation. Onset of symptoms in early infection is seen by 7 days and includes malaise, nausea, vomiting and abdominal pain. A missed diagnosis in pregnancy is common as other more common infections are suspected. The rash classically starts as a blanching macular rash at wrists and ankles and progresses to a non-blanching petechial rash that can become more confluent and progress to purpura. Occasionally, progression to peripheral gangrene necessitates amputation. Disease progression can be severe within days of onset and can result in multi organ dysfunction, hepatomegaly, confusion, meningismus and pneumonia.[143]

Studies in pregnant women are limited but the disease does not appear to be more severe compared with the general population. Vertical transmission has not been described. A case series of four patients in Mexico treated with doxycycline for RMSF had bad outcomes, with three mothers having spontaneous abortions in the first trimester, the fourth was a full-term spontaneous vaginal delivery (SVD).[144] The authors identified 10 cases in the literature including their four patients. Doxycycline was used in five cases, chloramphenicol in three and amoxicillin in two. Maternal fatality occurred in three cases, one case was complicated by amputation of digits due to gangrene and the remaining cases were uncomplicated. Three neonates died post-partum, and three pregnancies miscarried. Apart from one neonate that had transient hyperbilirubinaemia, the remaining three cases were uncomplicated. Use of amoxicillin in two cases was associated with fatality for both mothers and foetuses.

Diagnostic tools in early infection are limited. Serology is usually negative until day 10. IFA is the gold standard, with a fourfold increase in titres or convalescent titre $>1{:}64$ indicative of

infection. Currently, PCR is of limited utility due to low levels of circulating bacteria.

Doxycycline is the treatment of choice for a minimum of 5–7 days with treatment to continue until clinical stability and complete defervescence for 48–72 h. IV doxycycline is recommended for hospitalised patients with nausea, vomiting, decreased GCS and clinical instability. In pregnancy, chloramphenicol 50–75 mg/kg in four divided doses for 5–7 days can be used despite the risk of grey baby syndrome, and is also continued until afebrile for 48–72 h.[143]

Typhus

Epidemic typhus (ET) caused by *Rickettsia prowazekii* is a human louse-borne (*Pediculosis humanus*) illness that differs from ST and murine typhus (MT) as humans are the primary host of the infection, and were thought to be the only host until the bacterium was identified on the fleas of squirrel species.[145] This infection differs aetiologically from other typhus infections in the sense that it is not endemic to specific areas but increases in frequency at times of increased proximity of people, decreased sanitation, famine and war, similar to LBRF. Little is known about its specific picture in pregnancy.

ST and MT caused by *O. tsutsugamushi* and *Rickettsia typhi* have a wide geographic distribution. ST is a mite-borne infection (chiggers) with a distribution across the Asia-Pacific region from Afghanistan to Northern Australia. The mite, *Leptotrombidium*, affects rodents. Humans are accidental end hosts, and acquire the disease by a bite from the mite.[146] MT is a rickettsial infection of the rate flea, *Xenopsylla cheopis*, but can also affect cat and mouse fleas.[147] The infection is spread when human bites are inoculated with stool of an infected flea. MT is distributed across South-east Asia, North Africa, South America and Latin America.[148] Both diseases present as acute febrile illnesses, and are almost indistinguishable clinically apart from the frequency of the presence of an eschar on the patient.[149]

An 18-year cohort of febrile women in Thai-Myanmar, in an endemic area where 12.3% of all infections are thought to be caused by typhus,[150] identified 26 women with typhus by positive IFA, PCR or *in vitro* isolation of rickettsia spp. The authors compiled a case series of 96 pregnant women with typhus through a systematic literature review, their 26 cases and with 3 unpublished cases from their cohort that had a 4-fold rise in ST IgM titre; complete data were available for 87 women. Typhus resulted in higher preterm birth (14.3% *versus* 7.3%) and low birth weight (22.2% *versus* 17.4%) compared with outcomes of malaria in pregnancy in the same region.[151] Maternal death occurred in two patients (2.6%) and 17.3% of pregnancies under 28 weeks ended in miscarriage. Adverse outcome was seen in staggeringly high numbers in 62.5%, 42.9% and 54.1% in 1st, 2nd and 3rd trimesters, respectively. As azithromycin is effective therapy for typhus and is not contraindicated in pregnancy, 66% (61/92) of patients received monotherapy and all patients received azithromycin in combination with another antibiotic. A subsequent case series of ST in India echoed these findings; in one series of 33 patients, poor foetal outcome was seen in 51.5%, with the loss of foetus in 42.4%.[8] In another series of 42 patients, 33% of mothers had miscarriage significantly more frequently than the 2.8% loss in the background population.[152] A reason for increased adverse outcome in pregnancy may be the intrinsic affinity for vascular endothelial tissue and possible vasculopathy within the placenta, although this has never been shown.

In light of these serious adverse events in pregnancy, the potential risk *versus* benefit of using doxycycline may fall in favour of its use for gestational ST and MT. A randomised controlled trial (RCT) comparing azithromycin for 3 days (A3) *versus* doxycycline for 3 (D3) or 7 (D7) days in non-pregnant patients showed that azithromycin was definitively inferior to doxycycline for MT (22.5%, A3 *versus* 4.1% D3, 1.4% D7).[153] A systemic review of doxycycline has not shown correlation between doxycycline and teratogenic effects in pregnancy.[18] Previous ST papers alluding to doxycycline resistance in the 1990s were questionable and further studies were not done at that time; the paradigm of doxycycline resistance for ST is shifting and newer studies show this is not in fact the case.[154] Although ST does not appear to have the same issues of treatment inferiority to azithromycin as MT, azithromycin, doxycycline and rifampicin appear to have equal efficacy.[155]

Triatomine bug- and fly-borne diseases in pregnancy

Due to their geographical distribution, vector-borne infections like Chagas disease, trypanosomiasis, leishmaniasis and bartonellosis are commonly found in lower socioeconomic countries, and fall under the umbrella of neglected tropical diseases (NTDs). A lack of funding to develop quality and robust research studies, public health strategies and access to best pharmacological treatments confer a huge burden on the poorest members of society. Vector control is key to addressing the global burden of these diseases. A historical shift of infection control through understanding environmental and entomological factors to dependency on the insecticide-based unilateral control approach in the 1950s has cultured a vulnerability in our global strategy, with emerging insecticide resistance. A more cerebral, complex and locally tailored approach to NTDs is called for.[156,157] Addressing these diseases has immeasurable benefits, not just to the health of individuals but on a societal level to the prosperity of emerging nations, and economic and social issues like gender inequality.[158,159]

Chagas disease

Chagas disease (CD), also known as *Trypanosoma cruzii*, is a protozoal infection of Central and South America and is recognised as one of the NTDs with the biggest impact on human mortality and quality of life with 500,000 reported DALYs (disability-adjusted life years). The primary mode of transmission is a bite from the reduviid bug, subclasses *Triatima infestans* and *Rhodnius prolixans* being the most common vectors in South and Central America, respectively. CD can also be spread following organ transplantation, blood transfusion, and from contaminated food and water. Approximately 8 million people are infected and 10,000 people die annually from complications of this infection. Seroprevalence in endemic countries like Mexico have been estimated to be as high as 3.38% nationally, indicating that actual numbers of infected individuals may be far higher with as many as 8 million in Mexico alone.[160] Some areas of Bolivia still have seroprevalence rates as high as 70%. Traditionally a rural disease, the human impact on ecosystems has facilitated its spread to urban and peri-urban areas.

Congenital CD occurs in approximately 5% of infants born to mothers with CD, equating to a staggering 14,385 neonates in Latin America born with the infection yearly.[161] Despite its prevalence, few studies have looked at the impact of CD on fertility and adverse pregnancy outcomes. CD does not appear to have an impact on fertility. Maternal infection does not appear to be associated with negative outcomes but congenital infection is associated with prematurity, low APGAR scores, low birth weight, hepatosplenomegaly, anaemia and thrombocytopenia in newborns. Rarer complications can occur including meningoencephalitis, pneumonia and death.[161]

Current diagnostics for CD include direct visualisation of blood on film, and parasites can be visualised microscopically in those with high infectious load. At lower loads, blood products can be spun to form a pellet that can be visualised by microscopy. Visualisation of the placenta has low sensitivity and it has been suggested that up to one half of cases of congenital CD are missed for this reason.[162] Molecular studies, IFA and ELISA can also be used, but are not useful for infant diagnosis, as cross-over of CD DNA and maternal antibodies into the foetus can occur, and antibody can persist for up to 9 months and lead to false positive results. Children of seropositive mothers should be tested within the first month, and at 6 and 12 months. Screening with serology is valid only if tested positive after 10 months, in the absence of clinical disease.

Treatment of mothers is not recommended during the period of pregnancy or breastfeeding, and should be instituted only after this time period.[163] Administering benznidazole treatment to women of childbearing age in an endemic area has been shown to reduce vertical transmission of CD in a small observational study. It was found that 14% of children of 114 untreated women developed congenital CD compared with 0% of 61 treated women.[164] This may be a strategy to prevention congenital CD in national prevention programmes. Treatment of CD in children should be commenced as soon as possible with benznidazole and nifurtimox for no less than 60 days. Children treated within 1 year of diagnosis have good long-term outcomes.[163]

Trypanosomiasis

Trypanosma gambiense and *Trypanosoma rhodesiense* are trypanosomal protozoal illnesses in West and East SSA spread by the tsetse fly, and

are from a distinct clade separate from *T. cruzi* and far less impactful on pregnancy.[165,166] *T. gambiense* is the more severe variant of sleeping sickness and, although rare, vertical transmission has a much higher incidence with *T. gambiense*.[167]

Leishmaniasis

Leishmaniasis caused by the protozoa *Leishmania* is another NTD that has two forms: cutaneous and visceral (kala-azar). Three subspecies are known to cause the more severe visceral variant; *infantum, donovani* and *aethiopica*. Found in the tropics, subtropics and Southern Europe in an area populated by 380 million people, the vector of transmission is the sandfly. Immature promastigotes injected from the saliva of an infected fly invade host macrophages and mature into amastigotes. Subsequent infection of monocyte-rich tissue including liver, spleen, lymphatic system and bone marrow, and can result in systemic disease. Visceral leishmaniasis is the more severe variant and can cause fever, weight loss, hepatosplenomegaly and anaemia, and is generally fatal within 2 years without treatment.[168] Hepatosplenomegaly can be occult in pregnancy due to the enlarging uterus. Diagnosis is made by direct observation of parasites on biopsy of spleen, liver, bone marrow, IFA and ELISA. In pregnancy, sternal bone marrow biopsy is preferred over splenic or lymph node biopsy.

Vertical transmission is not as prevalent or well described as with other protozoal infections like CD; nonetheless, compelling cases of vertical transmission have been reported. A case series of five pregnancies describe hepatosplenomegaly in mothers who were all successfully treated with Liposomal amphotericin B without adverse outcome to the mother or foetus; and a further nine were described who did not have vertical transmission.[169] Also described in the series was a literature review identifying 17 other cases describing congenital infections in untreated mothers, with a mortality of 27% in newborns following vertical transmission. Liposomal formulations reach high concentrations in spleen and liver tissue but are expensive and difficult to procure in many endemic areas. Pentavalent antimony, the more commonly used therapy worldwide, is contraindicated in pregnancy due to a lack of data. Antimony is also prone to resistance and toxicity. Miltefosine a compound now used as a second line agent to Liposomal. Ampotericin B is also teratogenic and contraindicated in pregnancy.

Bartonellosis

Bartonellosis includes over 20 bartonella subspecies, with most human disease described as caused primarily by spp. *quintana, henslae* and *bacilliformis*. Fleas, lice and flies are all vectors for Bartonella spp. Chronic Carrion's disease and bacillary angiomatosis are cutaneous manifestations of the vector-borne disease caused by *B. bacilliformis*. Bartonella spp. can cause endocarditis in some populations and can manifest systemically with different syndromes, including cat scratch disease, trench fever, hepatic peliosis, bacteraemia, vasculitis, aneurysms, uveitis and neurological disorders.

Carrion's disease is the most deadly manifestation of bartonella, and has had a mortality as high as 88% in the pre-antibiotic era and 10% in recent times.[170] This includes the medical student of its namesake who self-inoculated with serous fluid from a verruga peruana in 1885, confirming the suspicion that Oroya fever and verruga puruana are the same aetiology.[171] Its vector is the sandfly, *Lutzomyia verrucarum*. The vector was confirmed in 1913 with the building of the Lima-La Oroya railway resulting in the death of thousands of workers who were bitten by sandflies harbouring this bacterium.[172] Unlike other infectious vector-borne diseases that have pan-continental distribution, Carrion's disease is seen exclusively in the Andes between 3000 and 10,000 feet, primarily in Peruvian valleys but also in Colombia. The disease is biphasic, with an initial acute presentation also known as the aforementioned 'Oroya fever,' and is characterised by fever, haemolytic anaemia and thrombocytopenia. A poorly understood transient T cell deficiency can lead to opportunistic superinfection, most commonly with species of enterobacteraceae, toxoplasmosis, *Pneumocystis jiroveci* (PJP), *Mycobacterium tuberculosis* (TB) and *Staphylococcus aureus* and has been reported in as many as 35% of cases.[173] Other complications include neurological sequelae including seizures, coma, pericarditis and myocarditis. A chronic variant exists characterised by raised papular cutaneous lesions, *verruga peruana*; only one phase may be present or both simultaneously are also possible. Populations with relative immune deficiency, like childhood and pregnancy, are particularly vulnerable to complications from this infection, especially bacterial sepsis.

Diagnosis is made by direct visualisation of intra-erythroycytic gram negative bacilli on giemsa-stained blood films, patients may have positive

blood cultures in the acute phase, and PCR is also used. Chronic phase diagnostics include biopsy of verrugae and serology. Treatment has traditionally been with chloramphenicol IV, ceftriaxone IV for severe disease or ciprofloxacin in non-severe disease.

In pregnancy, high mortality, miscarriages, preterm birth and foetal deaths are all caused by Carrion's disease in the acute phase. In a case series of two patients with acute bartonellosis, both patients survived and had SVD, but the authors allude to a case series of five patients, which resulted in maternal death in two patients, and miscarriage in another two.[174] Only case reports suggest vertical transmission. A 22-day-old presented with Oroya fever confirmed on blood by PCR, where the mother retrospectively had a febrile illness in the third trimester and was identified with vascular cutaneous lesion consistent with verruga peruana.[175] Other cases include a 19-day-old with Oroya fever, where the mother was also blood smear positive and a pre-term newborn of 90 min with a confirmed bartonellosis on blood culture in a mother with verrucous lesions. There is an overall paucity of reporting of Carrion's disease, especially in pregnancy. There is no animal model, and humans are the only known reservoir of Carrions disease.[176] Chloramphenicol is the mainstay of treatment for acute Oroya fever although combinations with quinolones and other antibiotics have been used.[173]

Discussion

We have described a variety of vector-borne illnesses that manifest in pregnancy, and discuss some of the issues related to our understanding, and sometimes a lack thereof, of the complex interaction of the organism(s), host and immunological factors, and the triad of mother, unborn child, and placenta. Many of these 'neglected' diseases also have 'neglected' science, and more needs to be done to understand the epidemiology, burden of disease worldwide, and the short- and long-term consequences of these infections to the mother and child dyad.

A successful and healthy pregnancy requires carefully coordinated communications between the mother and foetus. Immune cells and cytokine signalling pathways participate as mediators of these communications to promote healthy pregnancy. At the same time, certain infections or inflammatory conditions in pregnant mothers cause severe disease and have detrimental impacts on the developing foetus.[177]

Several theories have been proposed to explain the immunologic alterations that occur during pregnancy. Recently, it has been suggested that there is a shift from Th1 to Th2 immunity during pregnancy.[178] In addition to modification in the immunological response, insufficient attention is given to the placenta, which is an active immunologic site, capable of interacting with, and responding to, pathogens. Placental infection may elicit the release of inflammatory cytokines that activate the maternal immune system and lead to placental damage and miscarriage or preterm labour.[179]

Vaccine preventable infections contribute significantly to the burden of disease worldwide in terms of infection-related morbidity and mortality for pregnant women and their offspring. The strategy of maternal vaccination, and indeed vaccination of all women of childbearing age, will continue to be a priority, as current interventions (prevention and treatment with anti-infective agents) have had limited impact to date on many infections in pregnancy. We currently have vaccines for a number of vector-transmitted infections (i.e. Yellow fever, Dengue, Japanese encephalitis). These should be offered to all women of childbearing age in at risk populations. As we develop zika vaccines and malaria vaccines, there will be an opportunity to consider vaccination prior to and during pregnancy for appropriate at-risk populations.[180] It is important for the WHO, UNICEF, and other international organisations to protect the health of children worldwide, to acknowledge the important role that vector-borne infections are having globally on child health; new ICD11 codes must recognise and capture these infections in pregnancy. LD and other borreliosis infections are poorly understood in pregnancy; as are the NTDs vector-borne infections; a better characterisation of these infections in both high-income countries and resource-limited settings is critical.

Our approach to new drug development in modern times and the ethics of exclusion of safety and efficacy data for pregnancy needs to be reviewed. This issue was highlighted recently in the realm of therapy in human immunodeficiency virus (HIV)

and the distinct lack of data on new antiretroviral therapies.[181] The authors highlight the need for ethics committees to aid in promoting inclusion of pregnancy in new studies and the need to incentivize their inclusion. Overall better investment of monies and resources to study, understand, control and eliminate these infectious diseases spread by vector transmission will potentially have lasting benefits to the unborn children of the future.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics

Our study did not require an ethical board approval because it did not contain human or animal trials

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