The limited knowledge of placental damage due to neglected infections: ongoing problems in Latin America

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ABSTRACT

The placenta works as a selective barrier, protecting the fetus from potential infections that may affect the maternal organism during pregnancy. In this review, we will discuss several challenging infections that are common within Latin American countries and that may affect the maternal-fetal interface and pose risks to fetal development. Specifically, we will focus on emerging infectious diseases including the arboviruses, malaria, leishmaniasis, and the bacterial foodborne disease caused by Shiga toxin-producing Escherichia coli. We will also highlight some topics of interest currently being studied by research groups that comprise an international effort aimed at filling the knowledge gaps in this field. These topics address the relationship between exposure to microorganisms and placental abnormalities, congenital anomalies, and complications of pregnancy.

Abbreviations: ADE: antibody-dependent enhancement; CCL2: monocyte chemoattractant protein-1; CCL3: macrophage inflammatory protein-1 α; CCL5: chemokine (C-C motif) ligand 5; CHIKV: chikungunya virus; DCL: diffuse cutaneous leishmaniasis; DENV: dengue virus; GB3: glycolipid globotriaosylceramide; HIF: hypoxia-inducible factor; HUS: hemolytic uremic syndrome; IFN: interferon; Ig: immunoglobulins; IL: interleukin; IUGR: intrauterine growth restriction; LCL: localized cutaneous leishmaniasis; LPS: lipopolysaccharide; MCL: mucocutaneous leishmaniasis; NO: nitric oxide; PCR: polymerase chain reaction; PGF: placental growth factor; PM: placental malaria; RIVATREM: Red Iberoamericana De Alteraciones Vasculares Em Transtornos Del Embarazo; sVEGFR: soluble vascular endothelial growth factor receptor; STEC: shiga toxin-producing Escherichia coli; stx: shiga toxin protein; TNF: tumor necrosis factor; TOAS: T cell original antigenic sin; Var2CSA: variant surface antigen 2-CSA; VEGF: vascular endothelial growth factor; VL: visceral leishmaniasis; WHO: world health organization; YFV: yellow fever virus; ZIKV: Zika virus

Introduction

The placenta has many vital functions, such as transport of nutrients and respiratory gases and secretion of hormones, among other essential roles that allow healthy embryonic/fetal development. Another important placental role is to serve as a selective barrier, protecting the fetus from potentially deleterious infections that may affect the maternal organism during pregnancy (Burton et al. 2016). These infections affecting the fetus during pregnancy may result either from intra-uterine vertical transmission or from unexpected shifts within the intra-uterine microbiome.

While the maternal organism tolerates the allogeneic fetus, it must also protect itself against invading agents.
The new balance between placental tolerance and systemic protection is achieved via complex immune system modulating mechanisms, including depression of cell-mediated immunity with maintenance of normal humoral immunity. Some pathogens systemically present in the mother can take advantage of these circumstances, colonize the placenta, break the maternal-fetal barrier, and infect the fetus, placing the pregnant women as a population group at risk, due to their susceptibility to infectious diseases. Several different cell layers constitute the placental-blood barrier, including syncytiotrophoblast, discontinuous inner cytotrophoblast layer, basal lamina of the trophoblast, mesenchymal tissue of the villus, basal lamina of the endothelium, and endothelium of the fetal placental capillary. Accordingly, these layers are arranged in a physical fence to selectively prevent pathogens and cells crossing from the maternal circulation from entering the fetal environment.

On the top placental-blood barrier, acting as a defensive mechanism, are the Hofbauer cells, representing the first-line immune response in the placenta. These cells are placental resident macrophages with the ability to protect the placenta against pathogenic infection, preventing intra-uterine vertical transmission (Zulu et al. 2019). Although maternal immune cells do not cross this barrier, maternal immunoglobulins (Ig), including IgG, do further contribute to intra-uterine immune defense (Schneider and Miller 2010).

Pregnant women constitute a population group at risk due to their higher susceptibility to infectious diseases. Although not yet clarified, ‘susceptibility’ to infections in pregnant women is more often, but not exclusively, described for pathogens that have optional or mandatory intracellular life cycles, such as viruses (e.g., cytomegalovirus), bacteria (e.g., Listeria monocytogenes) and protozoan parasites (e.g., Toxoplasma gondii) (Medawar 1952; Robbins et al. 2010, 2012; Duaso et al. 2011; Zeldovich and Bakardjiev 2012; Berger et al. 2017).

The World Health Organization (WHO) listed some relevant neglected tropical diseases from around the world (WHO 2017). Among them, leishmaniasis and dengue, as well as several arbovirus-related diseases, are recognized to be vertically transmitted during intrauterine life. The Latin America region reports the highest number of dengue cases, with more than 2 million cases per year. Also, Latin America is among the regions that display the highest distribution of leishmaniasis, and Brazil has the highest incidence around the world.

Another vertically transmitted disease affecting Latin America is malaria. The impact of this condition is so widespread that the WHO supports the Global Malaria Programme, where 37 countries, including some Latin American countries, join efforts to control and eliminate malaria. While Paraguay and Argentina received the WHO certification as malaria-free countries; others, including Equator, Mexico, Costa Rica, and Suriname still report the occurrence of this infection (WHO 2019).

Another recent topic that has caught the attention of public health officials at WHO is bacterial foodborne diseases, and among them, infection with Shiga toxin-producing Escherichia coli (STEC). Of interest, it seems that STEC infection can also cause adverse pregnancy outcomes through vertical transmission (Sacerdoti et al. 2018). This type of foodborne infection is easily preventable by simple hygiene and food safety measures. Even so, the incidence of this disease is extremely high in Latin America, and Peru, Bolivia, and the Equator, are among the countries with most notable infection (Nations 2018).

In this review, we will analyze the emerging infections affecting the mother, which may impose deleterious effects on the placenta and, consequently, on fetal growth/development. We focus on infectious diseases that are considered public health challenges within Latin America countries, and that are currently being studied from a maternal-fetal perspective by research groups associated to RIVATREM (Red Iberoamericana de Alteraciones Vasculares em trans tornos del Embarazo), as part of an international effort to fill the knowledge gaps in this field. This investigative network seeks to strengthen the exchange of knowledge and scientific collaboration for the study of vascular problems associated with pregnancy disorders, with an emphasis on Latin America.

**Emerging and reemerging infections in Latin America**

**Arbovirus infections**

Arbovirus (arthropod-borne virus) infections are a current public health problem caused by viruses that are transmitted by arthropod vectors and are pathogenic to human beings. They belong to six leading main RNA virus families (Togaviridae, Flaviviridae, Bunyaviridae, Reoviridae, Rhabdoviridae, and Orthomyxoviridae) with high genetic variability (Charlier et al. 2017). Most arboviruses that cause disease in human beings display high similarity between the clinical aspects or even the absence of them, which can complicate their early diagnosis (Liang et al. 2015). The most common manifestations are fever, possibly associated with cutaneous, joint, neurological, or hemorrhagic symptoms and signs, although several arboviruses infections can be asymptomatic (Charlier et al. 2017).

Several arboviruses are currently associated with maternal and fetal pathologies, such as Chikungunya...
virus (CHIKV), Western equine encephalitis virus, Venezuelan equine encephalitis virus, Ross River virus, Dengue virus (DENV), Japanese encephalitis virus, West Nile virus, Yellow fever virus (YFV), Crimean-Congo hemorrhagic fever virus, La Crosse virus, and Rift Valley fever virus (Charlier et al. 2017). However, the arbovirus most studied in recent years due to the 2015–2016 outbreak in the Americas is the Zika virus (ZIKV), which received great worldwide attention due to the link with maternal infection and fetal microcephaly and other central nervous system abnormalities (Mlakar et al. 2016; de Araújo et al. 2018).

More recent studies demonstrated an association of other arboviruses, such as DENV and CHIKV, with poor neonatal outcomes such as meningoencephalitis, myocarditis, bullous skin lesions, and other clinical manifestations (Gerardin et al. 2014; Contopoulos-Ioannidis et al. 2018; Paixão, et al. 2018a). Although other infections associated with congenital disorders are included in prenatal screening, the lack of adherence to the prenatal care program or the incomplete screening for these infections, remain relevant health problems for the mothers and their babies in Latin America (Neu et al. 2015; Carvalho et al. 2019). In Brazil, for example, the Unified Health System still does not require ZIKV, DENV, or CHIKV serology or molecular biology tests in their prenatal screening tests, even after the recent outbreaks. The lack of standardized screening protocols leaves to the physician the decision whether to order arboviruses tests, in cases where patients present fever and rash during pregnancy.

Although many arboviruses infections result in adverse effects during pregnancy for both mother and child, their current impact during pregnancy is still being studied, and many questions remain to be answered, along with an accurate description of the incidence of adverse fetal outcomes and placental involvement. Furthermore, the pathophysiological mechanisms allowing ZIKV, DENV, and CHIKV to cross the placental barrier remain unclear.

**Zika virus (ZIKV)**

The ZIKV is a member of the Flaviviridae family, which was initially isolated in Nigeria in 1954 and has been detected since 2015 in the Americas, where it has been causing a worrisome number of cases of congenital brain abnormalities. Although the ZIKV epidemic in the Americas has ceased at present, the infection still constitutes a significant cause of concern, especially in pregnant women living in eco-epidemiologically prone areas (Rodriguez-Morales et al. 2018).

Maternal symptoms are generally low-grade fever, headache, and cutaneous rashes. ZIKV infection can also cause myalgia, arthralgia, and vomiting, all of which are also common symptoms of other arbovirus diseases (Mlakar et al. 2016; de Araújo et al. 2018). Moreover, ZIKV can also cause autoimmune neurologic complications such as Guillain-Barré syndrome, as well as acute disseminated encephalomyelitis in rare occasions (Franca et al. 2016; Suwanmanee and Luplertlop 2017).

During pregnancy, ZIKV transmission may occur vertically, by crossing the placental barrier and infecting the fetus, which will have a variety of symptoms and malformations depending on gestational age. ZIKV infections during the first trimester can cause the congenital Zika syndrome, which is characterized by stillbirth/miscarriage, intrauterine growth restriction (IUGR), as well as microcephaly, ventriculomegaly, and other brain malformations (Brasil et al. 2016; Franca et al. 2016). These conditions are caused indirectly by placental inflammation and directly by ZIKV replication in the fetal brain. Thus, several studies have detected ZIKV in fetal or neonatal brains, amniotic fluid, and placenta (Calvet et al. 2016; Driggers et al. 2016; Mlakar et al. 2016), meaning that this virus can be vertically transmitted during intra-uterine life, increasing both intra-uterine and new-born mortality.

Regarding the histopathological findings in ZIKV infected placentas, these vary from patient to patient, as well as according to the gestational trimester of infection. Among others, the most common findings were: chronic inflammation (TORCH type) with villitis, villous immaturity with the persistence of the cytotrophoblast layer and thickening of their basement membrane, edema and hyperplasia of Hofbauer cells, as well as some degree of hypervascularity and stromal fibrosis, and deciduitis (Noronha et al. 2016; de Noronha et al. 2018). Nevertheless, other studies reported that placentas infected with ZIKV did not have villitis, TORCH type inflammation, necrosis, or scarring, although confirmed the villous immaturity and Hofbauer cells hyperplasia (Rosenberg et al. 2017; Schwartz 2017). Moreover, the absence or significantly lesser amount of pathological changes in placentas from patients infected in the third trimester of pregnancy strongly suggests that the time of infection is relevant to finding histopathological alterations in the placentas.

Many studies using mouse models to address ZIKV infection in pregnancy have been published recently (Adibi et al. 2016; Aliota et al. 2016; Miner et al. 2016; Cao et al. 2017; Kam et al. 2017; Xavier-Neto et al. 2017; Regla-Nava et al. 2018). Those mouse models have successfully demonstrated that ZIKV infection
during early pregnancy resulted in infection of the placenta and the fetal brain, showing similar histopathological findings as ZIKV-infected human placentas (Paes et al. 2018). Also, ZIKV-infected mouse placentas presented poor pregnancy outcomes such as IUGR, miscarriage, and fetal demise (Adibi et al. 2016; Aliota et al. 2016; Miner et al. 2016; Sheridan et al. 2018), as well as neural tube defects, hydrocephalus, and arthrogryposis (Xavier-Neto et al. 2017), confirming the association between ZIKV infection and those complications observed in human epidemiological studies.

Other experimental approaches using in vitro human placental explants, and bi- and tri-dimensional culture models have confirmed ZIKV infection and replication in the placenta (Petitt et al. 2017; Weisblum et al. 2017). These studies focused on elucidating which kind of cells are the main placental reservoirs and how those cells would help ZIKV cross the placental barrier and spread into the developing fetus. Thus, first trimester placentas are prone to be infected, and particularly Hofbauer cells, mesenchymal cells, fibroblasts, and cytotrophoblast cells (both villous and extravillous), as wells as decidual cells and decidial macrophages were infected by ZIKV. Replication of ZIKV has been found mainly in Hofbauer cells (Costa MA 2016; Tabata et al. 2016; Aagaard et al. 2017; Weisblum et al. 2017). In comparison, at term, both syncytiotrophoblasts and cytotrophoblasts are more resistant to ZIKV infection, which could be due to a decrease in receptors used for viral entry, such as TYRO3 and AXL (Bayer et al. 2016; Jurado et al. 2016; Quicke et al. 2016; Aagaard et al. 2017; Sheridan et al. 2017). However, ZIKV replicates in placentas from all trimesters, with viral RNA load levels slightly higher in first trimester placentas than third-trimester placentas (Bhatnagar et al. 2017). Several trophoblast cell lines were also successfully proven to be infected by ZIKV (Aldo et al. 2016; Cao et al. 2017; Arumugasamy et al. 2018; Luo et al. 2018), modulating pro-apoptotic (Aldo et al. 2016) and pro-inflammatory (Ribeiro et al. 2018; Ma et al. 2018) pathways.

Since Jak/STAT and AKT-mTOR are also involved in brain pathogenesis and microcephaly development due to increased autophagy and suppression of the IFN response pathways (Ojha et al. 2018), some studies attempted to find therapeutic targets. Therefore, inhibiting autophagy by suppressing the Atg16L1 gene or by administering hydroxychloroquine can reduce vertical transmission of ZIKV in pregnant mice (Cao et al. 2017). Some studies also proposed administration of interferon (IFN)-γ during mid-pregnancy to promote host defense and reduce disease severity, as this cytokine was able to decrease ZIKV replication in JEG-3 cells, first-trimester human cytotrophoblast cells, and mouse models, as well as decreasing fetal malformations and demise (Chen et al. 2017; Corry et al. 2017). The immunological cross-reactivity between ZIKV and other flaviviruses was recognized in the past years by independent research groups. Interestingly, some of the flaviviruses antibodies are capable of cross-neutralization, but also to elicit antibody-dependent enhancement (ADE) of ZIKV infection (Priyamvada et al. 2016; Bardina et al. 2017; Fernandez et al. 2017; Kam et al. 2017; Willis and Hensley 2017; Hermanns et al. 2018; Brown et al. 2019). Thus, previous exposition to DENV is related to increased pathogenesis of ZIKV due to ADE, a phenomenon initially described between DENV serotypes (Bardina et al. 2017). Using Stat2 knockout mice, Brown and collaborators (2019) showed DENV antibodies increase ZIKV replication and pathogenesis during pregnancy, as well as inflammation in the placenta, regardless of gestational age, through FcγR in Hofbauer and trophoblast cells (Brown et al. 2019). Nonetheless, other studies showed antibodies against DENV prevented severe ZIKV infection and death in mouse models (Kam et al. 2017) or even presented therapeutic activity against ZIKV infection (Fernandez et al. 2017). Another phenomenon to be considered is DENV-specific CD8+ T cells, found to protect pregnant mice from ZIKV infection through a phenomenon known as T cell original antigenic sin (TOAS) (Regla-Nava et al. 2018).

The ZIKV epidemic began in 2007 in the western Pacific islands, followed in 2013–2014 by a larger outbreak in French Polynesia in the South Pacific. In Latin America, ZIKV emerged in 2015, mostly in Brazil, launching a public health emergency. Later, this infection spread to other countries in the Americas and the Pacific (Baud et al. 2017). Despite multiple studies in Brazil and other countries within the Americas, there are still many questions that should be addressed regarding the impact of ZIKV during pregnancy as well as on newborns and children exposed to this arboviral infection. For instance, an unsolved issue is the duration of viral persistence in mother and child (Villamil-Gomez et al. 2017), since viral RNA was detected in placentas after several weeks of maternal infection, indicating that the virus can persist in the placenta for extended periods following the onset of maternal symptoms (Rosenberg et al. 2017).

**Dengue virus (DENV)**

Dengue fever is a vector-borne disease caused by four distinct serotypes of the Dengue virus (DENV1, 2, 3, and 4) from the Flaviviridae family (Gubler 2002). Dengue has recently been one of the most critical public health issues in tropical and subtropical regions. Over the
past 50 years, dengue fever has progressively achieved the status of a pandemic, with approximately 4 billion people at risk of infection, an estimated 390 million cases and 20,000 deaths occurring annually, and both pregnant women and infants belonging to the high-risk group (Messina et al. 2015). Nevertheless, few reports exist on DENV vertical transmission, fetal abnormalities, and placental infection (Basurko et al. 2009; Ribeiro et al. 2013; Nunes et al. 2016; Ribeiro et al. 2017; Paixao et al. 2018a; Kallur et al. 2019). Among the most common adverse outcomes of maternal DENV infection are preterm birth, IUGR, and classical dengue fever symptoms in newborns (Basurko et al. 2009; Ribeiro et al. 2018; Kallur et al. 2019), also definitely associated with increased maternal and fetal morbidity and mortality (Kallur et al. 2019).

In a case report, DENV infection in a Brazilian woman at 12 weeks of gestation resulted in spontaneous abortion eight days after the start of Dengue fever symptoms. After examination, the presence of DENV was confirmed in several tissues of the aborted fetus: kidneys, lung epithelial cells, and ependymal ventricular cells in the brain (Ribeiro et al. 2013). Moreover, before the recent epidemic linking ZIKV with congenital neurological abnormalities, flaviviruses were not considered to be associated with congenital malformations in humans, until a recent report by Paixao and collaborators (2018a) that showed DENV was also associated with several brain malformations, increasing the odds of neurological abnormalities by 50% (Paixao et al. 2018a). Increased incidence of malformations in the fetal corpus callosum and holoprosencephaly were observed if Dengue fever occurred in the first trimester of pregnancy, as well as other alterations, such as congenital neurologic anomalies, anencephaly, encephalocele, microcephaly, congenital hydrocephalus, and other malformations of the brain and spinal cord (Paixao et al. 2018a). Interestingly, the hypothesis of an increased risk for neural tube defects after a Dengue fever outbreak was initially formulated in 1988 in India (Sharma and Gulati 1992), thirty years before the study from Paixao and collaborators. Also, since we now know DENV can also be vertically transmitted, some studies have shown placental alterations (Ribeiro et al. 2013, 2018; Nunes et al. 2016), such as cholangitis, villous hyper maturation, and edema, as well as general decidual and placental inflammation (Ribeiro et al. 2018).

Nunes and collaborators (2016) reported a case where DENV2 RNA was detected in umbilical cord blood and both NS1 and NS3 viral proteins were found in the placenta and umbilical cord from a 32–33 weeks pregnancy that ended in maternal and fetal death (Nunes et al. 2016). The NS3 protein was also found inside Hofbauer cells, as well as cytотrophoblast cells (Aagaard et al. 2017). Interestingly, using the HTR-8 SV/neo cells, Luo and collaborators (2018) showed DENV was able to infect them, and the viral RNA time-dependently increased in culture. Also, DENV infected cells produced cytokines such as IFN-γ, interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), IL-8, monocyte chemoattractant protein-1 (CCL2), macrophage inflammatory protein-1 α (CCL3) and chemokine (C-C motif) ligand 5 (CCL5) (Luo et al. 2018). The authors also reported that compared to ZIKV, DENV was able to replicate as efficiently as ZIKV, and to induce similarly high IFN responses, but lower inflammatory cytokine and chemokine levels. Using placental term explants, it was shown that a strain of DENV2 was able to infect placentas similarly to ZIKV, mainly increasing the production of IFN-γ and 4, IL-6, IL-1β, and IL-10, although no increase in cell death was observed, which means DENV might act through different pathways than ZIKV (Ribeiro et al. 2018).

DENV infection affected approximately 23 million Brazilians in the past four decades (Salles et al. 2018). Despite the high incidence of DENV infection in Latin America, studies investigating the impact of this infection during pregnancy on placental function are still largely lacking. A recent case report of a pregnant woman who presented complications due to DEVN infection, leading to maternal and fetus death in the 29th gestational week, indicated the presence of DENV protein in the maternal side of the placenta and revealed fetal organs abnormalities including inflammation (Nunes et al. 2019).

The case reports discussed above highlight recent maternal mortality statistics data showing that DENV infection increases the risk of maternal death three times, and hemorrhagic fever caused by DENV increases this risk 450 times (Paixao et al. 2018). This is a clear indication that DENV infection should be further studied in the context of pregnancy.

Another essential point will be the evaluation of future vaccines being developed against DENV infection and whether they are effective and safe during pregnancy, given that the sole vaccine currently commercially available is only indicated to seropositive subjects to prevent reinfection in endemic areas (Wildersmith 2019).

**Chikungunya virus (CHIKV)**

The CHIKV was initially isolated in the 1950s during an outbreak in Tanzania. Unlike DENV or ZIKV, CHIKV belongs to the *Togaviridae* family (Robinson 1955). Since its first isolation, three different genotypes were classified: the Asian, the East-Central South African, and the West African, according to

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genomic comparisons with phylogenetic analysis from originally reported regions (Wahid et al. 2017). The first vertical transmission was reported during the massive 2005–2006 outbreak on La Réunion Island, France (Economopoulou et al. 2009). The first Asian genotype case detected in the Americas was in the Caribbean island of Saint Martin in 2013 (Leparc-Goffart et al. 2014), whereas the first East-Central South African genotype was first isolated in Bahia state, Brazil in 2014 (Costa-da-Silva et al. 2017), where both strains started outbreaks through several American countries.

Regarding vertical transmission, the risk and impact of mother-to-child transmission of CHIKV are under review. Most of the knowledge derives from the experience of the massive outbreak caused by the East-Central South African genotype in La Réunion Island, where perinatal infection and several complications of neonatal illness were described (Ramful et al. 2007; Fritel et al. 2010). However, the Thailand 2009–2010 CHIKV outbreak is not related to maternal-vertical transmission or fetal alterations (Laoprasopwattana et al. 2016), which might be explained by different CHIKV strains.

Several studies indicated that CHIKV was able to cross the placental barrier, since maternal CHIKV infection in all trimesters resulted in fetal transmission in 15 to 50% of pregnancies (Senanayake et al. 2009; Gerardin et al. 2014; Torres et al. 2016), and was related to poor pregnancy outcomes, such as preterm births, IUGR, and spontaneous abortion (Senanayake et al. 2009; Gerardin et al. 2014; Dotters-Katz et al. 2015; Ramos et al. 2018). Fetal malformations are not frequent, but the newborn may display mild to severe infection symptoms, such as fever, irritability, rash, generalized edema, hyperalgesia, stiff neck, hemodynamic instability, exanthem, hemorrhagic disturbances, diarrhea, distal cyanosis, diffuse abdominal pain, hyperpigmentation, and bullous dermatosis (Senanayake et al. 2009; Torres et al. 2016; Escobar et al. 2017), but also meningoencephalitis, sepsis, respiratory failure and myocarditis in rare cases (Lenglet et al. 2006; Ramful et al. 2007; Torres et al. 2016). Another reason for concern is that CHIKV intrauterine infection is associated with postnatal-onset microcephaly, cerebral palsy, and seizures, as well as a long-term neurodevelopmental delay (Gerardin et al. 2014; Contopoulos-Ioannidis et al. 2018; Ramos et al. 2018).

Unfortunately, observations on changes in placental histopathology are not available, and only a few in vivo or in vitro studies are available regarding how CHIKV infected placental cells and crossed the placental barrier. A study conducted in mice showed that CHIKV was unable to surpass the placental barrier without breaches that allowed transfer of maternal blood to fetal circulation (Couderc et al. 2008), while another study found that CHIKV struggled to replicate in human decidua or villi explants, but still could infect cells and replicate, although slower than other related arboviruses (Platt et al. 2018). The limited number of studies available does not allow forming a conclusion on whether CHIKV causes substantive placental or fetal damage, despite all the evidence of vertical transmission in several countries, including in Latin America.

**Malaria**

Over 219 million cases of malaria were reported globally in 2017, resulting in nearly 435,000 deaths (Malaria 2019), with sub-Saharan Africa being the most affected region. Although some Latin America countries are currently in a pre-elimination phase, malaria is still present in specific regions within Latin America (Alimi et al. 2015).

Among people affected by malaria, pregnant women are one of the populations at highest risk, considering their altered cell-mediated immune response. So far, what we have learned is that the hormonal status induced by pregnancy modulates the immune response, and parasitemia tends to be ten times higher within pregnant women, promoting poor pregnancy outcomes and obstetric complications (Rogerson 2017). Thus, new insights about the pathophysiology of placental malaria are necessary to explore biomarkers in the early stages of the plasmodial infection during pregnancy, in places showing a high incidence of this infection, including some Latin American countries.

The occurrence of malaria infection in pregnant women is well-described (Nosten et al. 1991). Indeed, the occurrence of malaria infection is increased up to 10-fold in primigravidas living under holoendemic conditions (Brabin 1983). Malaria is caused by *Plasmodium falciparum* infection, considered as the central parasite infection associated with low birth weight in first pregnancies in Africa (Walker et al. 2014). In Latin American countries such as Colombia, gestational malaria occurs due to both *P. falciparum* and *Plasmodium vivax* (Arango et al. 2013). Moreover, malaria infection correlates with maternal mortality in endemic zones due to obstetric complications (GBD 2015 Mortality and Causes of Death Collaborators. 2016).

Malarial infection in the placenta, mostly known as placental malaria (PM), is characterized by sequestration of infected erythrocytes in the intervillous spaces, initiating a local inflammatory response (Rogerson et al. 2003). During PM, the histopathological changes observed include peri villous fibrinoid deposits, augmented thickness of the placental barrier (Souza et al. 2013), syncytial knotting, and leukocyte infiltration.
(Muehlenbachs et al. 2010; Carmona-Fonseca et al. 2013; Souza et al. 2013).

Indeed, these structural modifications, along with vascular alterations within the placenta, directly contribute to the high incidence of low birth weight and fetal death observed in pregnancies committed by PM (Ismail et al. 2000). (Machado Filho et al. 2014; Lopez-Perez et al. 2016)

During *P. falciparum* infection, erythrocytes express Var2CSA, a variant of *P. falciparum* erythrocyte membrane protein 1 (Fried and Duffy 1996). This protein enables erythrocytes to bind to chondroitin sulfate A, expressed on the cytotrophoblast surface (Fried et al. 2006). Var2CSA and other ligands promote erythrocyte sequestration and secretion of CCL2 and CCL-3 (Suguitan et al. 2003), favoring monocyte recruitment and placental macrophage activation, actions which amplify the immune response initiated against *P. falciparum*. Simultaneously, pro-inflammatory cytokines such as TNF-α and IFN-γ are released, enhancing the placental inflammation. In the case of *P. vivax*, the search for specific proteins that promote adherence to placental tissue is still unresolved (Carvalho et al. 2010).

Furthermore, infiltration of leukocyte populations results in augmented oxygen consumption, which, combined with the reduced placental blood perfusion, culminates in increased expression of several factors including hypoxia inducible factor-1 (HIF-1α), vascular endothelial growth factor (VEGF), as well as its receptors (VEGFR-1 and sVEGFR-1) (Boeuf et al. 2008). Conversely, decreased placental growth factor (PGF) expression is observed. As a consequence, this inflammatory environment favors adverse gestational outcomes, resulting in placental insufficiency and therefore, intrauterine growth restriction (Fried et al. 1998; Boeuf et al. 2008). (Agudelo et al. 2014)

Other immune system components are also involved in PM. For example, in acute malaria infections, an increase of component 5a from the complement system was found (Conroy et al. 2009), eliciting angiogenic disturbances in the placenta (Conroy et al. 2011, 2013; McDonald et al. 2015).

**Leishmaniasis**

Leishmaniasis is a chronic disease caused by several species of protozoa from the *Leishmania* genre, mainly transmitted through the bite of infected vectors. *Leishmania sp.* are unicellular organisms belonging to the class Kinetoplastida and the family Trypanosomatidae, that infect humans and multiple other mammals. The leishmaniasis infectious process results in a broad spectrum of clinical manifestations or disease forms, classified as localized cutaneous (LCL), diffuse cutaneous (DCL), mucocutaneous (MCL), and visceral (VL) manifestations. These forms also differ from each other according to the species of the parasite involved, genetic predisposition, and the host’s immune system vulnerability (Desjeux 1996; Bastos 2012; Gurung and Kanneganti 2015).

Although classically leishmaniasis occurs via phlebotomes transmission, the occurrence of leishmaniasis in several regions where the presence of phlebotomines has not been reported suggests alternative routes of transmission, including sexual (venereal) and transplacental (vertical) transmission, with the latter already shown to be responsible for causing VL in mice (Nuwayri-Salti N 1985), dogs (Riera and Valladares 1996; Rosypal et al. 2005; Silva et al. 2009; Naucke and Lorentz 2012; Ben Slimane et al. 2014), and humans (Symmers 1960; Meinecke et al. 1999; Pagliano et al. 2005; Boehme 2006; Zinchuk and Nadraga 2010).

The first described case of congenital transmission of leishmaniasis occurred in England (Low 1926). Even though the pregnant woman remained infected throughout the gestational period, gestation was not compromised and there were no unfavorable symptoms. However, after birth, the child began to show clinical manifestations such as anemia and splenomegaly, and necropsy demonstrated the presence of *Leishmania donovani*, observed in spleen aspirates. A few years later, another case report described the presence of the parasite responsible for the visceral form of the disease in both the mother and the preterm newborn, arguing that congenital transmission contributed to premature childbirth (Nykundi et al. 1988).

Immunocompromised patients, mostly HIV-infected, are currently subjects of study because of the increased risk of VL co-infection. This fact is of particular interest in developing countries, since the simultaneous presence of these two infections changes the natural course of the clinical manifestations, making it difficult, among other issues, to diagnose and treat both diseases. Similar to these patients, pregnant women are also becoming increasingly targeted by intracellular parasites such as those of the genus *Leishmania*, due to their immune response adaptation, which indeed confers a predisposition to reactivation of these parasites, leading to the aggravation of cutaneous lesions and fetal complications such as premature births and stillbirths (Morgan et al. 2007; Pagliano et al. 2016). Another likely form of transplacental transmission is the parasite-mediated degradation of the trophoblast, as occurs with *Trypanosoma cruzi* and *Toxoplasma gondii* (Medawar 1952; Robbins et al. 2010, 2012; Duaso et al. 2011; Zeldovich and Bakardjiev 2012; Berger et al. 2017).
Although there are some speculative comments on placenta being adapted to resist infection by pathogens, especially from maternal blood (Robbins et al. 2010), placental findings such as late maturation, chronic infarction, and ischemic changes in placental villi were described in a woman with VL, even in the absence of the parasite in this organ. Also, it has been considered that the disease may be associated with placental development and efficacy of the pregnancy (Caldas et al. 2003).

The non-classical cutaneous leishmaniasis transmission is less studied, because in this case, the parasites are predominantly found in cells of the phagocytic system and externally in the skin or in mucosal tissues, where the clinical symptoms of the disease occur. However, this does not make it impossible for the parasite to colonize other organs, such as the placenta and it is possible for parasites to reach the Hofbauer cells, considered as the central lineage of Leishmania target cells in this organ (Costa et al. 2005; Reithinger and Dujardin 2007; Romero et al. 2010).

In this sense, congenital transmission and invasion of the placenta by Leishmania parasite, reported in animals studies and humans placenta (Eltoum et al. 1992; Avila-Garcia et al. 2013; Mescouto-Borges et al. 2013), may change the placental structure and lead to villous vessel thrombosis and trophoblastic degeneration of the placenta (Eltoum et al. 1992; Baergen 2011), which are associated with outcomes such as severe maternal disease, preterm labor, intrauterine growth restriction, and fetal demise (Baergen 2011; Agrawal and Hirsch 2012; Robbins and Bakardjiev 2012; Kemp 2014).

Moreover, Leishmania chagasi DNA was detected by polymerase chain reaction (PCR) in 49% of placentas of symptomatic and asymptomatic dogs, indicating that although the placenta is probably not a target tissue for Leishmania infection, it serves as a transmission route for the fetuses, mainly because the placenta is highly vascularized. Leishmania mexicana is transplacentally transmitted and causes fetal death, implantation loss, and reduction of the bodyweight of offspring, demonstrating the importance of identifying the species that cause the cutaneous form of the disease as potentially able to cross the placental barrier and affect fetal health (Pangrazio et al. 2009; Avila-Garcia et al. 2013).

The capacity of Leishmania for placental invasion and congenital transmission via the transplacental route is also associated with the maternal immunological environment (Maspri et al. 2016; Berger et al. 2017). On one hand, the production of inflammatory cytokines, such as IL-12 (Park et al. 2002), IL-1, IFN-γ, TNF-α (D’Oliveira et al. 2002), and IL-2 contributes to activation of macrophages and parasite elimination. On the other hand, parasite replication and persistence are related to the development and production of IL-4, IL-5 and IL-13, leading to susceptibility to the Leishmania infection (Sacks and Noben-Trauth 2002; Von Stebut et al. 2003; Bailey and Lockwood 2007; Scott and Novais 2016).

Besides, infection in a murine model resistant to cutaneous leishmaniasis caused by Leishmania major increased the frequency of fetal resorptions and failures in fetal implantation in vivo, and this was associated with decreased IL-10 production and increased IFN-γ by the spleen and popliteal lymph node cells in vitro (Krishnan et al. 1996). Therefore, upon parasite infection during pregnancy, an expected Th1 lymphocyte response is changed in direction to Th2 lymphocyte activation.

Currently, leishmaniasis has a wide geographic distribution, being present in the Americas, Europe, Africa and Asia, and is generally associated with poverty, malnutrition, population displacement, and climatic and environmental changes. Worldwide prevalence of 12 million cases is estimated, with an annual incidence of around 50,000 to 90,000 new cases of VL, and between 600,000 and 1 million new cases of LCL. In the Americas, cutaneous leishmaniasis is endemic in 18 countries and 892,846 new cases have been reported in the period 2001–2016 (Mitropoulos et al. 2010; PAHO 2019).

Although leishmaniasis is a neglected disease, probably due to its low economic appeal, and although experimental and clinical evidence on leishmaniasis is even scarcer in pregnant women, this population should not be neglected, as they are vulnerable to the sequelae of leishmaniasis, which may even contribute to fetal outcomes. Although of significant prevalence, the scarcity of data on this topic shows that much needs to be studied, both by scientists and public health authorities, to be able to characterize the impact that the different types of parasites of the genus Leishmania exert during the whole process of pregnancy, in the short and possibly long term, in both mothers and fetuses.

**Shiga toxin-producing escherichia coli**

Shiga toxin-producing Escherichia coli (STEC) is a significant public health problem due to the contamination of food and water supplies. STEC is present in the intestinal tract of healthy cattle, and transmission to humans that occurs by consumption of undercooked ground beef, manure-contaminated water, vegetables, and direct transmission from person to person (Hussein 2007).

STEC produces a gastrointestinal infection that may manifest as diarrhea and hemorrhagic colitis. STEC can
produce two antigenically diverse forms of Shiga toxin proteins (Stx1 and Stx2) and their variants, where Stx2 is more virulent and epidemiologically more relevant than Stx1 (Palermo et al. 2009). Once ingested, STEC colonizes the human intestine and releases Stx. This toxin crosses the epithelial barrier, reaching the systemic circulation and the target organs, mainly kidney and brain, and causing, among others, hemolytic uremic syndrome (HUS) (Karmali et al. 1983). HUS is characterized by thrombocytopenia, hemolytic anemia, acute renal failure, and central nervous system alterations. The massive HUS outbreak in 2011 in central Europe caused by a novel Stx2-producing STEC affected more adults than children (Frank et al. 2011).

Up to now, there is no specific treatment for HUS patients. The prevention of STEC infections and development of HUS principally depends on the appropriate cooking of food, avoiding cross-contamination, and the consumption of pasteurized dairy products (Thomas and Elliott 2013).

Regardless of the mechanism of Stx action, Stx may bind to glycolipid globotriaosylceramide (Gb3) receptors on the endothelial cell surface, undergoing endocytosis through receptor-mediated internalization, followed by retrograde transport to the Golgi apparatus, and finally, inducing cell death by inhibition of protein synthesis and consequent cellular apoptosis (Raa et al. 2009).

Infections during pregnancy have been associated with a higher incidence of spontaneous abortion, preterm birth, or placental dysfunction (Romero RC, T. 2002; Baud and Greub 2011). However, the risks of spontaneous abortion or preterm birth in humans related to STEC infection are unknown or poorly understood. There are scarce reports of neonatal HUS caused by STEC transmission from mother to the newborn during delivery (Steele et al. 1984; Ulinski et al. 2005; Stritt et al. 2013) and a few cases of STEC-mediated HUS during pregnancy (Tanaka et al. 2000; Chart et al. 2002).

In vitro studies using the WISH cell line derived from human amniotic tissue showed that both Stx1 and Stx2 induce apoptosis (Yoshimura et al. 2002). Additionally, Stx2 impairs cell migration, invasion, and endovascular differentiation in extravillous trophoblast cells (Scalise et al. 2019).

Furthermore, it has been demonstrated that intrauterine injection of Stx2 in pregnant rats during early gestation leads to spontaneous abortion and perinatal complications, possibly linked with direct action of the toxin on placental tissues, which finally results in maternal morbidity and pregnancy loss (Sacerdoti et al. 2014). Stx2 binds to the placental microvasculature and decidual cells through GB3 receptors, eliciting placental hypoxia, and IUGR (Sacerdoti et al. 2015). As in other target organs, Stx2 also enhances placental inflammation, making the cells more sensitive to the toxin (Ibarra et al. 2013). Additionally, the injection of Stx2 and lipopolysaccharide (LPS) in pregnant rats increases nitric oxide (NO) and prostaglandin production in the placenta, leading to preterm delivery of dead fetuses (Ogando et al. 2003; Aisemberg et al. 2007; Burdet et al. 2010). Also, Stx2 increased circulating levels of TNF-α, altering the balance of cytokines at the maternal-fetal interface required for the proper placentaation process (Burdet et al. 2013). Moreover, Stx2 can also cause spontaneous abortion in mice by damaging trophoblasts and producing intrauterine hemorrhage, fibrin deposition, and neutrophil infiltration (Yoshimura et al. 2000).

HUS is widely distributed around the world, with a low incidence rate (1–3 cases/100,000 children <5 years) (Nataro and Kaper 1998; Varela et al. 2008; Torres et al. 2018). In contrast, in South America, HUS is endemic, with an incidence 10-fold higher than in the rest of the world. In Chile and Uruguay, less than 10 cases per 100,000 children of 5 years of age were reported annually (Cordovez et al. 1992; Torres et al. 2018). In Argentina, HUS is highly prevalent, with an incidence of 10–17 cases per 100,000 children less than five years of age, and lethality of 1 to 4% (Rivas et al. 2014). This illness is recognized as the most common cause of acute renal failure in children and the second leading cause of chronic renal failure (Repetto 1997, 2005).

During pregnancy, several forms of thrombotic microangiopathy may occur because of HUS. In these patients, HUS drastically compromises the maternal kidney function, and this condition is worsened by the absence of specific and efficient treatments (Brue et al. 2017). Since many of the causes of spontaneous abortion and preterm delivery are still unknown, it is reasonable to presume that STEC infections during pregnancy, either symptomatic or asymptomatic, maybe one of the causes for those perinatal complications. It is important to remark that in pathological processes such as fetal growth restriction, spontaneous abortion, preeclampsia, and preterm delivery are associated with inflammation and hypoxia. Thus, asymptomatic STEC infections might be involved in the etiology of these pregnancy disorders.

**Concluding remarks**

The Sustainable Development Goals of the United Nations organization include ‘to reduce the global...
maternal mortality ratio to less than 70 per 100,000 live births and end preventable deaths of newborns and children under five years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births (The United Nations Development Program (UNDP) 2019). Over the past 20 years, substantial efforts were made to drastically reduce both maternal and neonatal mortality rates within most Latin America countries. Besides cardiovascular complications, which are among the most frequent causes of maternal and fetal mortality all over the world, neglected microorganisms represent significant contributors to disturbances observed during and after pregnancy in Latin America and other low-income countries. However, these conditions are frequently not addressed to the level that they require.

**Arbovirosis:** The recent events linking ZIKV infection to the occurrence of newborn microencephaly resulted in a tremendous effort from Latin America research groups to reveal the mechanisms involved in the deleterious effect of ZIKV infection during pregnancy. Even the international scientific community embraced the cause seeking out answers, considering the gravity of this epidemic. A common point linking these topics is how these issues related to ZIKV infection during pregnancy are necessary, including the construction of a network to support children with microencephaly and their families; the elucidation of therapies that could limit fetal damage upon infection; educational campaigns for the population, aiming reduction of ZIKV and other arbovirosis' transmission and early recognition of symptoms; the development of tools for fast diagnostic; limiting the spread of these viruses around the world; creation of collaborative scientific networks, favoring multicentric studies; prioritization of financial resources to increase the knowledge in this field; among others actions is required.

**Malaria:** the target set by the United Nations organization is to reduce case incidence by at least 90% until 2030 and to eliminate malaria in at least 35 countries. The delay of several countries to pay attention to this disease and its occurrence in areas with difficult access has made the battle against malaria even harder. Efforts are necessary to diagnose asymptomatic infected subjects, considering that only 10-20% of infected people are currently diagnosed. Early diagnostic associated with appropriate treatment can limit malaria transmission. Additionally, it is necessary to improve the search for new therapies and address drug resistance.

**Leishmaniasis:** Economically, leishmaniasis can be incredibly debilitating, since injuries can be mutilating, creating a social stigma. Therefore, combatting poverty is another critical point that should be addressed to prevent a disease that affects people with limited financial resources. The development of more effective vaccines and new therapies should be encouraged. Indeed, currently available treatments elicit severe side effects, and most of the time, require hospitalization for intravenous administration. The accuracy and speed of diagnosis are also aspects that challenge the reduction of leishmaniasis around the world. The adaptative capacity of these parasites represents a critical obstacle for addressing leishmaniasis adequately. Collaborative networks, such as the Kldrug-R project between Europe and India, represent important initiatives aiming to gain understanding in these fields.

**STEC:** Several domestic and wild animals are STEC reservoirs. However, ruminants are the major STEC reservoir, and in most cases, they are asymptomatic. Considering that some Latin American countries are prominent meat exporters, good practices both from producers and consumers are required to avoid food contamination. Special populations, including children, pregnant, and older people are more susceptible to the deleterious and permanent effects of this infection. Although the incidence of STEC is relatively low, some Latin American countries, including Argentina, Chile, and Uruguay, display a high incidence of this infection, and the severity of symptoms associated with sequelae justify further research on this topic.

A common point linking these topics is how these conditions affect the placenta. A brief overview of the data reviewed is presented on Table 1 and Figure 1. In this regard, it has been commonly considered that the human placenta fulfills multiple functions including a physical and immunological barrier that prevents the exposure of the embryo/fetus to microorganisms that could compromise its wellbeing and life. Likewise, the presence of pathogenic microorganisms in the placenta has been associated with congenital anomalies and complications of pregnancy, such as IUGR and preterm delivery. Therefore, considering the placenta as a critical protective element during pregnancy, further studies should directly address this organ during the occurrence of these and other infections.
Some points of interests should be further addressed for the cited diseases including, but not only: how these infections affect the placental structure, disrupting the protective barrier conferred by this organ; the occurrence of genetic polymorphisms of drug placental transporters within Latin America population, within transporters used by the drugs currently used to treat these conditions; to elaborate or standardize clinical protocols, considering the classification of drugs used to treat these conditions according to the risk during pregnancy, and also the pharmacokinetics and pharmacodynamic alterations observed throughout the pregnancy; the development of alternative pharmacological treatments to replace drugs that display high rate of resistance or risk of use during pregnancy; the development of point of care tests, to rapidly diagnose these conditions in a noninvasive way, to include the serological screen for significant congenital infections, including arboviruses, during prenatal care.

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**Table 1. In vitro and in vivo studies in a placental model.**

| Infection                  | Model                  | Experimental model in placenta and results                                                                                                                                                                                                 |
|---------------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zika                      | Swan 71 cells          | Swollen mitochondria and increased apoptotic bodies with increased caspase-3 activation (Ma et al. 2018).                                                                                                                                       |
|                           | HTR-8 SV/neo cells:    | Induce the production of IL-6, IL-8, TNF-α, and CCL2 (Corry et al. 2017).                                                                                                                                                                   |
|                           | Placental term         | An increase in the production of IFN-β, IFN-γ, IFN-γ1 and IFN-4, IL-6, IL-1β, TNF-α and IL-10, also showing increased caspase-3 cleavage and cell death (Bardina et al. 2017).                                |
|                           | explants               |                                                                                                                                                                                                                                           |
| Dengue Virus              | HTR-8 SV/neo cells:    | Produced mainly IFN-β, IL-6, TNF-α, IL-8, CCL2, CCL3 and CCL5 (Corry et al. 2017).                                                                                                                                                           |
|                           | Placental term         | Increased the production of IFN-γ 1 and 4, IL-6, IL-1β and IL-10, no increase in cell death (Chen et al. 2017).                                                                                                                              |
|                           | explants               |                                                                                                                                                                                                                                           |
| Chikungunya Virus         | Mice: Maternal blood  | Virus was unable to surpass the placental barrier without breaches that allowed transference (Lenglet et al. 2006).                                                                                                                    |
|                           | to fetal circulation.  | Virus struggled to replicate in human decidual or villi explants, but still could infect cells and replicate (Coudrec et al. 2008).                                                                                                                   |
| Malaria                   | Human placenta         | Express receptor to infected erythrocytes, increased expression of hypoxia-inducible genes and inflammatory mediators (Suguitan et al. 2003; Fried et al. 2006).                                                                            |
| Leishmaniasis             | Rats                   | Increased the frequency of fetal resorptions and failures in fetal implantation, and this was associated with decreased IL-10 production and increased IFN-γ cells (Costa et al. 2005).                                      |
| Shiga toxin-producing     | WISH cell line:        | Both Stx1 and Stx2 induce apoptosis (Hussein 2007).                                                                                                                  |
| Escherichia coli          | Swan 71                | Stx2 impairs cell migration, invasion and the endovascular differentiation in extravillous trophoblast cells (Palermo et al. 2009).                                                                                                      |
|                           | Rats                   | Spontaneous abortion and perinatal complications, increase of NO, induce the production of TNF-α (Karmali et al. 1983).                                                                                                               |

Abbreviations: CCL2: monocyte chemoattractant protein-1; IFN: interferon; IL: interleukin; NO: nitric oxide; Stx: Shiga toxin proteins; TNF-α: tumor necrosis factor alfa.

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**Figure 1.** Main placental alterations associated with infection. In orange, the description of placental alterations caused by Arbovirosis, including chronic inflammation, deciduitis and villus disruption. In blue, the description of placental alterations caused by Malaria, including placental insufficiency, fibrinoid deposits and inflammation. In green, the description of placental alterations caused by Leishmaniasis, including late maturation, chronic infarction and ischemic changes. In yellow, the description of placental alterations caused by Shiga toxin-producing *Escherichia coli*, including placental dysfunction, intrauterine hemorrhage, fibrin deposition and neutrophil infiltration.
Considering that the conditions addressed here represent emerging health conditions, which in most cases do not attract the attention of pharmaceutical industry or consolidated research groups, the establishment of cooperative networks addressing common points of interest may be innovative, as a strategy to unite expertise and resources to accomplish more robust investigative work in Latin America. These networks may also favor fund-raising strategies and strengthen research proposals, in an international effort to fill some knowledge gaps observed in the Latin American population. These diseases have significant research potential and joint research actions need to be extended to these and other emerging conditions.

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Authors contributions

Manuscript writing (Leishmania): IMR, PCSS; manuscript writing (Arboviruses infection): AUB, ELLT; manuscript writing (Placental Dysbiosis and Microbiota): AC, AMA; manuscript writing (Malaria): JB, OA; manuscript writing (Introduction and Conclusion remarks): RGR, PA-R; manuscript writing (Shiga toxin-producing Escherichia coli): FS, AED, CI; project development, conceptualization, writing – review & editing: CE, TS, FRG; manuscript writing (Leishmania) and project administration: VVL.

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