Infections at the maternal–fetal interface: an overview of pathogenesis and defence

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Abstract | Infections are a major threat to human reproductive health, and infections in pregnancy can cause prematurity or stillbirth, or can be vertically transmitted to the fetus leading to congenital infection and severe disease. The acronym ‘TORCH’ (Toxoplasma gondii, other, rubella virus, cytomegalovirus, herpes simplex virus) refers to pathogens directly associated with the development of congenital disease and includes diverse bacteria, viruses and parasites. The placenta restricts vertical transmission during pregnancy and has evolved robust mechanisms of microbial defence. However, microorganisms that cause congenital disease have likely evolved diverse mechanisms to bypass these defences. In this Review, we discuss how TORCH pathogens access the intra-amniotic space and overcome the placental defences that protect against microbial vertical transmission.

Infections during pregnancy can be associated with devastating consequences to the pregnant mother and developing fetus. Vertical transmission, defined as infection of the fetus from the maternal host, is a major cause of morbidity and mortality in pregnancy. In some cases, bacterial, viral and parasitic infections induce dire outcomes in the fetus. The sequelae of infections in pregnancy include teratogenic effects, which cause congenital anomalies; growth restriction, stillbirth, miscarriage and neonatal death; prematurity; and maternal morbidity (Fig. 1). Vertical transmission of pathogens across the maternal–fetal interface can cause fetal infection, which can disrupt organogenesis and is associated with congenital anomalies of every major organ system (Table 1). Congenital anomalies are present in ~3% of live births and the proportion attributable to infection is poorly characterized1–2.

Pregnancy loss through miscarriage or stillbirth (defined as intrauterine fetal death after 20 weeks) can also be caused by infection. Approximately 10–30% of all stillbirths have an infectious aetiology1–2, although the low rates of diagnostic testing for infections in pregnancy might result in an underestimation of this value. The rate of pregnancy loss is variable with gestational age at infection and by specific pathogen. For example, infection with Treponema pallidum causes pregnancy loss or fetal death in up to 50% of cases1 whereas parvovirus B19 infection causes pregnancy loss or stillbirth in <3%. The mechanisms of pregnancy loss in the setting of ‘TORCH’ (Toxoplasma gondii, other, rubella virus, cytomegalovirus, herpes simplex virus) infections can be pathogen mediated, placenta mediated and/or can be through inflammation-induced preivable delivery. There are also outcomes of congenital infections that do not manifest until after delivery. These can include hearing loss, developmental delays and/or blindness as detailed below.

Inflammation initiated by an infection of the maternal host is also a known cause of preterm labour and can result in preivable delivery or sequelae of prematurity10 with lifelong consequences to the neonate. Neonates can have sequelae from maternal infections even with full-term development11, demonstrating that the fetal response to infection is not restricted to effects of prematurity. Early onset sepsis, an important cause of neonatal morbidity and mortality particularly in premature or low birthweight infants, is strongly associated with maternal infection12–14.

In this Review, we highlight the molecular pathogenic mechanisms of select pathogens that have distinct effects during pregnancy. The acronym TORCH was coined to refer to pathogens known to traverse the maternal–fetal barrier and cause congenital disease in the fetus15. In addition to the traditional TORCH pathogens, we also describe the pathogenesis of emerging pathogens with important sequelae to the pregnant person, fetus and/or neonate.

Placental structure and defences
To understand the mechanisms of vertical transmission, it is crucial to understand the unique structure and function that exist at the maternal–fetal interface. The human
placenta is a complex organ composed primarily of specialized fetus-derived cell types. As gestational age-specific differences in placental structure and cellular composition have been reviewed in detail elsewhere, we provide a concise description of human placental structure and development below to provide a framework to address mechanisms of pathogenesis. An overview of the structure of the maternal–fetal interface is shown in Fig. 2a.

The human placenta develops when the fetus-derived trophoblasts, the main cell type that comprises the placenta, form the trophectoderm (Fig. 2b). The trophectoderm forms a cellular barrier early in development to prevent infection of the embryo. The process of placental development continues rapidly from that point onwards and is not fully complete until the end of the first trimester, undergoing a series of remarkable morphological changes (reviewed in Ref. 18). These changes result in the development of chorionic villi, which form the primary contact between the fetus-derived placenta and the maternal blood supply that will eventually bathe these structures.

Trophoblast stem cells give rise to cytotrophoblasts (CTBs), the proliferative mononuclear cells of the placenta, and the syncytiotrophoblast (STB), a multinucleated contiguous cell layer that covers the entire surface of placental chorionic villi. During the first trimester, the placenta undergoes substantial morphological changes that result in the villous structure it will have for the remainder of pregnancy (Fig. 2b). The end of the first trimester also marks the crucial transition to a haemochorial placenta, wherein maternal blood directly contacts the fetus-derived placenta. This process requires extravillous trophoblasts (EVTs) to remodel the maternal microvasculature, which will ultimately allow for delivery of maternal blood to the surface of the placental chorionic villi. This is a crucial point as we discuss mechanisms of microbial vertical transmission, which could differ markedly between the first trimester, when there is no direct contact between the placenta and maternal blood, and the later stages of pregnancy once the haemochorial placenta is established.

The STB is the foremost barrier against the haemochorial spread of infectious agents, particularly from the point of the establishment of a haemochorial placenta. As the proliferative CTBs lie subjacent to the STB, they also benefit from the protection of this fused cell layer. Chorionic villi contain additional barriers to infection that reside in the villous stroma, including fetus-derived macrophages (Hofbauer cells) and the fetal microvasculature, which must be breached for an infectious agent to reach fetal blood. Recent work also suggests that maternally derived immune cell types are in close proximity to the fetus-derived placenta and may thus impart an additional layer of immune protection. Thus, when considering mechanisms of microbial vertical transmission, it is important to remember that transmission to the fetus requires infection of multiple cell types and/or breaching of cellular barriers, the most formidable of which is

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**Transplacental transmission**

- Placental disruption
- Fetal–maternal haemorrhage

**Transmission across fetal membranes**

- Ascending infection
- Sexual transmission

**Maternal impact**
- Increased inflammatory response
- Sepsis
- Respiratory distress
- Obstetric haemorrhage
- Death

**Placental impact**
- Decreased nutrient/oxygen transport
- Reservoir for reinfection
- Preterm labour

**Fetal impact**
- Growth restriction
- Birth defects
- Blindness/deafness
- Microcephaly/neurodevelopment
- Bone marrow suppression
- Fetal demise

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Fig. 1 | Routes of transmission across the placenta and consequences of infection. a | TORCH (Toxoplasma gondii, other rubella virus, cytomegalovirus, herpes simplex virus) pathogens can access the intra-amniotic compartment through multiple mechanisms, including direct transplacental transmission, placental damage or disruption and/or fetal–maternal haemorrhage. In addition, pathogens can be transmitted by ascending the genital tract. b | Infections in pregnancy can affect the maternal host, fetus and/or the placenta itself. The results of infection and the inflammatory response have consequences at each site.
the STB, as is discussed below. Given its central role in protecting the fetus, it is perhaps not surprising that the placenta has evolved highly efficient mechanisms of anti-microbial defence. In the following sections, we review key physical and immunological mechanisms of placental defence from infection.

Physical defences
As described above, the STB covers the entirety of the chorionic villous surfaces. The STB contains upwards of 60 billion nuclei and has a surface area of 5 m² in mid-gestation and 11–12 m² at full-term — a single cell layer roughly the size of a small bedroom! The very nature of the fused STB provides a powerful barrier to microbial transmission, given that many pathogens bypass other cellular barriers by directly or indirectly weakening cell–cell junctions (reviewed in Ref. 21). In addition to a complete lack of cell junctions, the surface of the STB also poses a barrier to microbial attachment and invasion given the presence of a dense cortical actin network subjacent to the brush border (Fig. 3). Thus, the shared physical nature of the STB provides common structural

| Pathogen | Mode of transmission | Hallmarks of congenital infection |
|----------|----------------------|----------------------------------|
| **Bacteria** | | |
| Listeria monocytogenes | Contaminated food | Stillbirth/pregnancy loss; preterm delivery; neonatal sepsis |
| Treponema pallidum | Sexual | Stillbirth/pregnancy loss; low birthweight; fetal hepatosplenomegaly; developmental delay; saddle nose deformity; rhinitis; dental deformities; chorioretinitis; anaemia; rash; dilated bowel; skin thickening; periostitis; bone fractures and demineralization |
| Streptococcus agalactiae | Commensal | Neonatal sepsis |
| Staphylococcus aureus | Commensal | Neonatal sepsis |
| Escherichia coli | Commensal | Neonatal sepsis |
| **Viruses** | | |
| Cytomegalovirus | Faecal–oral | Chorioretinitis; low birthweight; hearing loss; developmental delay; anaemia/thrombocytopenia; rash; stillbirth/pregnancy loss; ventriculomegaly; microcephaly; intracerebral calcification; echogenic bowel/abdominal calcifications; normal |
| Herpes simplex virus 1 and 2 | Sexual or oral contact | Neonatal meningitis; dermatological lesions; ventriculomegaly; microcephaly; intracerebral calcifications; chorioretinitis; optic atrophy; limb dysplasia |
| Varicella zoster virus | Respiratory droplets | IUGR; limb abnormalities |
| Lymphocytic choriomeningitis virus | Fomites (rodent based) | Ventriculomegaly/hydrocephalus; developmental delay; motor and sensory deficits; chorioretinitis; hearing loss |
| Zika virus | Arbovirus (Aedes species, sexual, blood borne) | Microcephaly; IUGR; hepatosplenomegaly; intrahepatic calcifications; ventriculomegaly; intracerebral calcifications; echogenic bowel; stillbirth/pregnancy loss |
| West Nile virus | Arbovirus (Culex species) | Chorioretinitis; meningitis/encephalitis; possible lissencephaly |
| Rift Valley fever virus | Arbovirus (Aedes species, Culex species, Anopheles and Mansonia species, contact with contaminated animal materials) | Stillbirth/pregnancy loss; preterm delivery |
| Human parvovirus B19 | Respiratory droplets | Anaemia; hydrops; stillbirth/pregnancy loss |
| **Parasites** | | |
| *Plasmodium falciparum* | Arthropod vector (Anopheles species) | IUGR; preterm delivery; severe hypoglycaemia |
| *Plasmodium vivax* | | |
| *Toxoplasma gondii* | Ingestion of contaminated food or oocytes | Ventriculomegaly; hydrocephalus; intracerebral calcifications; choroid plexus cysts; hydrocephalus; ascites; IUGR; hepatosplenomegaly |
| *Trypanosoma cruzi* | Arthropod vector (Triatominae subfamily) | IUGR; respiratory failure; hepatosplenomegaly; meningitis; heart failure; hydrops; heart disease; megacolon |

IUGR, intrauterine growth restriction; TORCH, *Toxoplasma gondii*, other, rubella virus, cytomegalovirus, herpes simplex virus.
mechanisms to resist diverse microorganisms. However, it should be noted that the STB is not the sole cellular barrier present in the human placenta. The stroma of the placenta also contains defensive barriers, including the microvasculature of fetal blood vessels, which would also need to be breached for microorganisms to access fetal blood. The physical defences of the villous surface restrict the attachment and/or invasion of non-viral pathogens, including *Listeria monocytogenes* and *T. gondii*22–24, but viruses appear to be capable of entering primary trophoblasts, suggesting that some viruses might overcome the physical barriers to microbial entry25–28.

**Immunological defences**

**The decidua.** The maternally facing surface of the placenta is in direct contact with the decidual lining of the uterus, and this leukocyte-rich layer is one of the first lines of immune defence at the maternal–fetal interface. The maternal decidua is in direct and/or indirect contact with fetal membranes, placental villi and the maternal circulation. The decidua can be divided based upon these contact sites — the decidua parietalis lines the uterine wall; the decidua basalis is the site of implantation and villous contact; and the decidua capsularis encases the fetal membrane. The decidual layers contain cytotoxic, helper and regulatory T cells, natural killer (NK) cells, innate lymphoid cells, macrophages and neutrophils29,30. Up to 40% of all decidual immune cells are leukocytes in the first trimester, and a leukocyte-rich infiltrate is also seen in parturition30–32. The composition of decidual cell populations displays gestational age-specific variation and is important for trophoblast invasion and for maintaining and establishing the placental vascular bed33,34. As such, particularly in...
the first trimester, decidual cells remain in close proximity to invading EVTs, and provide maternally derived immune defences at these sites (reviewed in Ref. 35). Despite its composition as an immune cell–enriched site, the decidua has been suggested to be a key reservoir for TORCH pathogens. Use of decidual explants and data from pathological examinations of clinical specimens suggest that the decidua may be a primary site of replication for several TORCH pathogens including cytomegalovirus (CMV)36, Zika virus (ZIKV)37 and L. monocytogenes38, and could thus form a reservoir for pathogens at the key site of the maternal–fetal interface.

The interaction of the decidua with various pathogens in vivo is complex, as decidual leukocytes have distinct phenotypic differences from those in the peripheral circulation. Maternally derived decidual macrophages exhibit unique properties compared with other macrophages resident in tissue or systemically circulating monocytes19,30,39,40. Studies suggest that the decidual composition of immune cells and their interaction with trophoblasts may alter their susceptibility to pathogens. For example, decidual NK cells possess the remarkable ability to transfer granulysins to trophoblasts to protect from L. monocytogenes infection without actively killing these cells41. These and other studies highlight the often unique and complex strategies of antimicrobial protection that exist at the maternal–fetal interface.

The immune cells in the decidua are in contact with decidual stromal cells, which can influence immune cell behaviour. In particular, the immune cell–rich decidua has altered activity in models of co-culture, reflecting that the complex architecture of the immune cell network within the decidual stroma modulates the immune inflammatory response. For example, decidual stromal cell function is altered with co-culture with macrophages42, dendritic cells and NK cells in a prostaglandin–dependent manner43. Moreover, the response of decidual stromal cells to pathogen stimulation is different from that of endometrial stromal cells44–46, suggesting that the microenvironment of the placenta has a role in innate immune defences. Decidual explants have been used to demonstrate that CD8+ effector memory T cells and NK cells can regulate decidual stromal CMV47 and herpes simplex virus (HSV)48 infections. These multicellular interactions are difficult to dissect and model but have important implications for understanding the immune landscape at the maternal–fetal interface as each individual component (for example, stromal cell regulation, hormonal microenvironment, composition of leukocytes) might have a role in immune defence against infection.

**Fig. 3 | Placental defences against pathogens.** Given its role as a primary barrier to the haematogenous spread of infectious agents, the human placenta has evolved disparate and non-overlapping mechanisms of antimicrobial defence. These can be separated into at least three categories, physical defences (left), the constitutive release of antimicrobial effectors (middle) and/or robust innate immune response to infection (right). Physical defences include the lack of cell–cell junctions of the syncytiotrophoblast layer; preventing inflammation-mediated damage of intercellular junctions that could compromise the integrity of this barrier. Additional physical defences include the dense cortical actin network lying sub-apical to the dense brush border of the syncytiotrophoblast. Another form of defence involves the constitutive release of potent antimicrobial effectors such as antiviral microRNAs in extracellular vesicles, cytokines (for example, type III interferons), and antimicrobial peptides (middle). The placenta also responds to pathogens with potent innate immune signalling, which further enhances the release of antimicrobial defence substances (right).
**Chorionic villi.** Fetal immune cell populations in placental development and in pregnancy-associated pathologies have been reviewed elsewhere\(^\text{22-24}^\text{,}^\text{61}\); therefore, we limit our discussion in this section to specific trophoblast-derived defensive strategies.

In addition to providing a physical defence from infection, it is also clear that villous trophoblasts form a chemical barrier to microbial vertical transmission. Trophoblasts have robust innate immune activity and secrete immunomodulators that are important for restricting infection (Fig. 3). In the case of viral infection, human trophoblasts constitutively release antiviral interferons that restrict infection in both an autocrine and a paracrine manner\(^\text{21,22}^\text{,}^\text{32}\), which appears to be specific for the STB. The release of interferons is a highly unique feature of trophoblasts as interferons are generally only induced in response to the detection of a viral infection. As the antiviral effectors of the interferon pathway, interferon-stimulated genes (ISGs), can exert potent cytotoxic and pro-inflammatory properties.

Trophoblast-derived interferons are exclusively those of the type III interferon family: IFNλ1, IFNλ2 and IFNλ3. In mice, type III interferons also confer protection from infection. As the antiviral effectors of the interferon pathway, interferon-stimulated genes (ISGs), can exert potent cytotoxic and pro-inflammatory properties.

Infection in mice protect against vertical transmission\(^\text{53,54}^\text{.}^\text{\textdagger}\). The type III interferon-mediated restriction of infection in mice is tightly associated with gestational age, with the greatest protection occurring after placentation\(^\text{21,22}^\text{.}^\text{\textdagger}\). Moreover, IFNλs delivered prophylactically or therapeutically in the setting of ZIKV infection in mice protect against vertical transmission\(^\text{53,54}^\text{.}^\text{\textdagger}\).

In addition to interferons, human trophoblasts also secrete antiviral microRNAs that are packaged into placentonal exosomes, which confer broad antiviral protection in non-placentonal recipient cells and can be isolated from the serum of pregnant women\(^\text{25,51,55-57}^\text{.}^\text{\textdagger}\). Given these non-redundant and potent antiviral defences, it is perhaps not surprising that most viruses are unable to directly replicate in the STB. However, it should be noted that the effects of type I interferons (IFNα and IFNβ) may be distinct from those of the type III interferons. Induction of maternal type I interferon signalling has been shown to damage the placenta in mice in vivo and in human ex vivo tissue explants\(^\text{49}^\text{.}^\text{\textdagger}\). Although the mechanisms for these opposing effects have yet to be fully elucidated, at least one ISG, interferon-induced transmembrane protein (IFITM), inhibits fusion of CTBs with the STB\(^\text{21,60}^\text{,}^\text{\textdagger}\), which may indicate that the expression of this and perhaps other ISGs must be tightly regulated in the placenta to prevent interferon-mediated damage.

In the case of bacterial or parasitic infection, many studies highlight the resistant nature of the STB, which has largely been attributed to physical barrier properties\(^\text{22-24,61}^\text{.}^\text{\textdagger}\). However, similar to the properties of antiviral resistance, it is clear that the human placenta also uses additional molecular pathways to resist infection by non-viral pathogens. In addition to the constitutive release of antiviral interferons, the human placenta secretes other cytokines that likely function to limit infections in both an autocrine and a paracrine manner. For example, the constitutive activation of the inflammasome in placental trophoblasts results in the constitutive release of cytokines, including IL-1β, IL-18 and IL-1α, which can be found circulating systemically in pregnant women\(^\text{62}^\text{.}^\text{\textdagger}\). In addition, infection of human placentals explants with *L. monocytogenes* robustly induces inflammasome signalling, the inhibition of which sensitizes trophoblasts to infection\(^\text{42}^\text{.}^\text{\textdagger}\). Like the effects of interferons, the paracrine effects of inflammasome-associated cytokines also protect from infection, as placenta-derived IL-1β primes circulating immune cells for subsequent inflammasome activation and protects from *L. monocytogenes* infection\(^\text{42}^\text{.}^\text{\textdagger}\). By contrast, inflammasome activation in the STB has also been implicated in increased severity of neonatal outcomes associated with placental malaria\(^\text{43}^\text{,}^\text{\textdagger}\), suggesting that similar to interferon signalling, the balance of this signalling is crucial.

There is no evidence to suggest that placenta-derived secreted products defend against parasite infections directly. In fact, the same placenta-derived factors that protect against viruses exert no effect on *T. gondii* infection\(^\text{46}^\text{.}^\text{\textdagger}\). Instead, in the case of *T. gondii*, the placenta releases diverse immunomodulatory factors including the regulatory T cell chemokine T cell chemokine 22 (CCL22) and CCL17 in response to infection\(^\text{53}^\text{.}^\text{\textdagger}\) (Fig. 3). However, the impact of this signalling on maternal and/or fetal consequences of infection has yet to be defined.

**TORCH pathogens**

As discussed above, TORCH pathogens make up a limited number of microorganisms with known teratogenic effects. In the following sections, we review key members of this group that fall into the categories of bacteria, viruses and parasites, and the consequences of these infections (Table 1).

**Bacteria**

*Listeria monocytogenes.* *L. monocytogenes* is a small Gram-positive bacterium that is transmitted through contaminated food. Listeriosis in pregnancy causes pre-maturity and stillbirth and enhances maternal morbidity with increased rates of meningitis and sepsis during pregnancy (Table 1). In a recent outbreak in South Africa, the mortality rate for infants was 28% and for pregnant women it was 8%\(^\text{64}^\text{.}^\text{\textdagger}\). Pregnancy-associated morbidity during this outbreak was responsible for 50% of cases presenting to health care\(^\text{64}^\text{.}^\text{\textdagger}\). Despite the immaturity of the fetal immune system in early pregnancy, treatment of *L. monocytogenes* in the first trimester after exposure has been shown to improve fetal outcomes\(^\text{65-67}^\text{.}^\text{\textdagger}\). By contrast, treatment after the first trimester has not been definitively shown to change the course of the disease for the fetus but is recommended to improve maternal outcomes\(^\text{65}^\text{.}^\text{\textdagger}\). This is likely due to enhanced susceptibility of the fetus to *L. monocytogenes* infection after the first trimester and suggests that there are gestational age-specific differences in vertical transmission.

After entry through the enteric mucosa, *L. monocytogenes* spreads cell to cell by manipulating actin polymerization. The mechanism of transplacental transmission of the bacterium remains unknown. In ex vivo cultures, the STB is highly resistant to infection\(^\text{24,65}^\text{.}^\text{\textdagger}\). The bacterial
virulence factors required for entry into other cells (for example, listeriolyis O and internalin B) are not required for entry into human choriocarcinoma trophoblast cell lines\(^{83}\). The bacterial internalin protein InlA is important for binding to E-cadherin on primary trophoblasts\(^{83}\), but its role in crossing the placental barrier in vivo remains unclear, with differential effects in different animal models\(^{82,83}\). Together, these data suggest that transmission across the placental barrier may require additional, yet uncharacterized, bacterial virulence factors. Accordingly, there was minimal strain variation with respect to the ability to infect the placenta in studies using a competitive in vivo model in guinea pigs\(^{84}\), suggesting that the trophoblast-specific virulence factors are conserved in epidemic strains.

After placental colonization, the bacterium spreads to fetal tissues and can be reseeded back to maternal organs\(^{85}\). In mice, actin polymerization through the bacterial protein ActA has been shown to be important for cell-to-cell spread and transmission across the maternal–fetal interface\(^{86}\). The secreted bacterial colonization factor internalin P is important for distorting cells and allowing the bacteria to traverse the basement membrane\(^{87}\), but the mechanisms of transport across the STB to the basement membrane have yet to be characterized. Importantly, fetal infection is associated with placental abscess development and innate immune cell recruitment to the maternal–fetal interface\(^{88}\). Studies in non-human primate models demonstrate that the bacterium is not required to traverse the maternal–fetal barrier to cause placentation, fetal loss and compromise\(^{89}\), suggesting that pregnancy loss may also occur in the absence of bacterial colonization of the fetus.

*Treponema pallidum*. *T. pallidum* is a well-characterized teratogen. This bacterium is 6–20 μm in length, has a small genome of only 1,041 open reading frames and has an outer membrane covering a layer of peptidoglycan but minimal surface-exposed proteins and no lipopolysaccharide\(^{90}\). The lack of surface proteins may facilitate evasion of the immune response and the remarkable longevity of the bacterium in the human host\(^{91}\). *T. pallidum* can colonize and cause disease in all fetal organ systems and is the causative agent of congenital syphilis (Table 1). More than 50% of women with syphilis have adverse pregnancy outcomes\(^{90,92}\), and fetal transmission causes a wide variety of neonatal pathologies including meningitis, osteochondritis, bone marrow suppression and hydrops\(^{91–95}\). Congenital syphilis is on the rise in the United States, with a reported 1,306 cases in 2018 (Ref.\(^{89}\)) and is a major cause of infection-mediated fetal loss and neonatal morbidity in the developing world, causing an estimated 150,000 stillbirths, 60,000 neonatal deaths and 100,000 infections of infants annually\(^{91,92}\).

The pathophysiology of *T. pallidum* congenital transmission remains largely unknown. The sequelae of the fetus with congenital syphilis depends both on the maternal stage of infection and the gestational age of the fetus\(^{94,95}\). Congenital transmission occurs less frequently with subsequent pregnancies, an observation known as Kassowitz’s law. This observation suggests that the maternal immune response to *T. pallidum* can limit the frequency of congenital syphilis, but the vertical transmission risk is never eliminated\(^{95–99}\). This has also been shown in a guinea pig model of congenital syphilis, which is the best-described model for this phenomenon\(^{90}\). Additionally, in the guinea pig model, the fetal IgM response corresponds more with vertical transmission than spirochaetal DNA\(^{31}\), suggesting that the fetal immune response is important in the pathogenesis of congenital syphilis.

Inflammation and maceration of placental tissue has been demonstrated in cases of pregnancy loss or intraterine fetal demise associated with congenital syphilis in the absence of congenital anomalies, suggesting that the up to 50% fetal loss rate associated with maternal syphilis might be attributed to the inflammatory response at the placenta itself\(^{92,93}\). Along with this, the Jarisch–Herxheimer reaction (heightened inflammatory responses that occur with antibiotic treatment of syphilis in pregnancy) is associated with preterm contractions and evidence of uteroplacental insufficiency\(^{91}\), suggesting that placental inflammation has a role in the pathogenesis of preterm delivery associated with syphilis.

As discussed above, the placenta forms a barrier that effectively restricts many bacterial pathogens. Although there is evidence that systemic inflammation can cause preterm birth and fever itself can be teratogenic, there is no evidence that other bacterial pathogens (for example, *Klebsiella* species, methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*) routinely traverse the placental barrier and cause fetal infection. These pathogens are important causes of maternal morbidity in the setting of systemic maternal infection (for example, *pyelonephritis*), but are not major causes of fetal infection, suggesting that the maternal–fetal barrier to multiple bacterial pathogens remains uncompromised in the case of maternal systemic illness and bacteremia. The mechanisms underlying the antibacterial defences of the placenta in the setting of bacteremia remain largely uncharacterized.

By contrast, there is a subset of well-described bacterial pathogens that ascend the genital tract and cause *chorioamnionitis* (reviewed in Refs\(^{95,96}\)). Intra-amniotic infection classically occurs in the setting of ruptured membranes, which suggests that the bridge of the fetal membrane provides an important barrier to fetal infection. Pathogens endemic to the vaginal microflora such as group B *Streptococcus* (GBS), *E. coli* and *Bacteroides* species have been found in placental and neonatal cultures\(^{97}\). Both primate and murine models demonstrate that vaginal microorganisms can traverse the genital tract and cause disseminated disease in the fetal cavity. Typically, infections arise from genitourinary microbiota and can be polymicrobial\(^{97,98}\). To cause disease in the uterine cavity, these bacteria would have to ascend the vaginal microbial biofilm and the antimicrobial cervical mucous plug to contact the fetal membranes and cause an inflammatory response locally.

The best-studied microorganism associated with ascending infection and neonatal disease is GBS, which...
Atrophy

the eye.

inflammation of the choroid

an abnormally small

condition in which the brain

Ventriculomegaly

of the skin are missing.

Aplasia cutis

A condition in which parts

tof the skin are missing.

Pericytes

Specialized connective cells

of mesenchymal origin that

classically surround endothelial

cells in blood vessels.

Aplasia cutis

A condition in which parts

tof the skin are missing.

Ventriculomegaly

A condition in which the brain

ventricles are abnormally large.

Microcephaly

An abnormally small

circumference.

Chorioretinitis

Inflammation of the choroid

surrounding the retina of the eye.

Atrophy

Degenerative and small.

can cause neonatal sepsis with transmission. Screening

for colonization and intrapartum prophylaxis with antibi­
totics decreases the incidence of early onset neonatal

sepsis98. GBS biofilms on fetal membranes have been

observed99 and it is one of the most commonly cultured

bacteria in the setting of intra-amniotic infections100. GBS

colonizes the genital tract in ~10–30% of women101. The

predilection of some isolates to cause neonatal

disease remains unclear, but GBS activates the innate

immune neutrophil and macrophage response to initiate

cytokine release, cell migration and the development of

extracellular traps and bacteriolysis102,103. The mecha­
nisms of pathogenic switching and specific virulence

determinants for ascending the genital tract include

pili, adhesins and altered regulatory systems (reviewed

in REFs 104,105). E. coli can also adhere to fetal membranes,

although to a lesser degree than GBS106. E. coli, like GBS,

inhabits the genital and gastrointestinal tract and is com­

monly isolated in the setting of intra-amniotic infection.

With implementation of universal screening and

intrapartum prophylaxis with antibiotics to GBS, E. coli

has become the most common aetiological agent of

late-onset sepsis in neonates107. In obstetric isolates,

phylogenetic subgroups are variable but genes on path­

ogenicity islands for type I fimbrae and iron acquisition

are enriched108, suggesting that horizontal gene acquisi­
tion is important to cause disease in pregnancy. Similar to

other bacterial pathogens, the specific virulence factors

that allow E. coli to cause clinical disease and ascend the

reproductive tract during pregnancy remain

under-studied.

Viruses

Both DNA and RNA viruses can traverse the maternal–
fetal interface and cause fetal disease. In the following

sections, we discuss key teratogenic viruses and what is

known regarding their routes of transplacental transmis­
sion and clinical outcomes. Although rubella virus was

a major source of congenital disease before successful

vaccination efforts, we have restricted our discussion to

the most common viruses currently associated with con­
temporary congenital disease — CMV, HSV1 and HSV2,

parvovirus B19, HIV and ZIKV (TABLE 1).

Cytomegalovirus. CMV is a member of the Herpesviridae

family and is one of the most common causes of verti­
cal infections globally. It is the single most common cause

of congenital hearing loss in the United States, and the

global burden of disease is also high, although likely

underestimated109. Like other herpesviruses, CMV

enters a latent state after acute infection and can be sub­
sequently reactivated. In the setting of maternal primary

infection, there is a ~40% risk of fetal transmission.

By contrast, the risk of transmission to the fetus after

reactivation is <0.05%, but causes most of the clinical

disease110,111. Gestational age-specific variation in infect­

cy and fetal consequences have been described112,

suggesting that alterations in the maternal–fetal inter­

face during gestation regulates the mechanisms of CMV

vertical infection. Placental histology in congenital

CMV infection ranges from normal to acute and chronic

intervillositis113. The classic, owl’s eye viral inclusion

bodies occur more frequently in the first and second

trimesters than in full-term placenta114.

Given that other recent reviews have provided thor­
ough overviews of the mechanisms by which CMV

might be vertically transmitted115–117, here we provide a

more focused overview. CMV has been shown to infect

trophoblasts, but with substantial gestational age-related

differences in infectivity18. Given that human CMV does

not readily infect rodents, in vivo studies of the mecha­
nisms of CMV vertical transmission are limited to

human placent al primary cell cultures and/or explant

models. Although guinea pig models of CMV infections

in pregnancy have been described118, these do not fully

recapitulate the phenotype of human CMV infections

during pregnancy. Studies of CMV infection in human

tissue demonstrate active replication in maternally

derived decidua, which may generate a viral reservoir

that could enhance the likelihood of CMV crossing

the fetal barrier in the setting of primary infection119,120.

Specifically, apolipoprotein B mRNA-editing enzyme

catalytic polypeptide-like 3A (APOBEC3A) has been

implicated in control of CMV replication in the decidua,

but not in placental villi121. Studies have also shown that

CMV may preferentially infect placental pericytes to gain

access to the fetus and that this might be a primary mode

of infection in the setting of maternal viremia122. The

role that these cells have at the maternal–fetal interface

remains largely uncharacterized, but they may represent

an important site from which CMV can traverse the pla­

centa and cause congenital infection particularly with

advancing gestation.

Herpes simplex virus. HSV1 and HSV2 can be transmit­
ted to the fetus via the transplacental route, but trans­
mission through contact with a virus-shedding lesion

in the genital tract is a far more common mode of verti­
cal transmission. HSV1 and HSV2 are neurotropic and

lie dormant in the dorsal root ganglion after primary

infection. On reaching the fetus, these viruses are highly

teratogenic and are associated with the classic triad of

manifestations in skin (aplasia cutis, scarring, erosions),

central nervous system (ventriculomegaly, microcephaly,

intracranial calcifications) and eyes (chorioretinitis,

atrophy), along with skeletal manifestations and fetal loss.

A mouse model recapitulates vertical transmission, with

fetal loss, congenital malformations and neurotropism,

demonstrating that haematogenous dissemination

(rather than ascending infection) is responsible for

effects on the fetus123.

The mechanisms of transplacental transfer of HSV1

and HSV2 are largely uncharacterized. The STB is

resistant to HSV1 and HSV2 infection, but EVTs are

permissive124,125. Although the HSV entry mediators

HveA, HveB and HveC are expressed in EVTs, viral

transmission is not blocked by antibodies to HveA126.

The maternal surface of the placenta is positive for

HSV1 or HSV2 in 9–28% of women who are asympto­
matic at the time of delivery without evidence of fetal

transmission127,128, suggesting that the placenta and/or

maternal immune response presents a barrier to trans­
placental transmission in women with non-primary

infection.
**Parvovirus B19.** Parvovirus B19 is a non-enveloped single-stranded DNA virus in the *Parvoviridae* family. Infection with parvovirus B19 is common during childhood, causing low-grade fever, maculopapular rash and slapped cheek facial rash. Humoral immunity is protective against infection, and 70% of the adult population is immune. The rate of transmission of maternal parvovirus B19 infection to the fetus is 17–33%, and most fetuses have spontaneous resolution with no sequelae, although ~3% can go on to develop non-immune hydrops from fetal anaemia. Fetal loss and stillbirth are associated with infection even in the absence of hydrops. The sequelae of infection vary with gestational age, such that infection after 20 weeks confers a 0.5% risk of fetal loss, whereas before 20 weeks the rate is increased 30-fold.

Parvovirus B19 exhibits strong tropism for erythroid precursors and immunohistochemistry demonstrates that after traversing the placenta the virus reaches the fetal endothelium. The parvovirus B19 VP2 capsid protein has been shown to bind to globoside, which is present on the surfaces of the STB and CTBs. The VP2 capsid protein has also been shown to bind to villous trophoblast cells through globoside glycolipids. After viral entry, non-structural protein 1 (NS1) induces apoptosis in cells. Consistent with this, apoptosis has also been demonstrated in the placenta in severely affected pregnancies, suggesting that fetal demise in the absence of hydrops may result from placental damage that directly affects function. The rare but classic sequela of parvovirus B19 is non-immune fetal hydrops caused by transient, severe anaemia with loss of both erythrocytes and nucleated erythroid precursors. Dichorionic twin discordance in infection and in clinical sequelae has been reported, suggesting that the placental and fetal responses are important for limiting clinical disease, but the immune mechanisms by which this occurs are unclear.

**HIV.** Congenital transmission of HIV remains associated with global neonatal morbidity. HIV can be vertically transmitted via the transplacental route, during delivery and/or through breastfeeding postnatally. In the absence of antiretroviral therapy (ART), ~25% of infants born to HIV-positive women become infected compared with <2% of those whose mothers are on ART. The relative contributions of the various routes of vertical transmission suggest that each has a role in congenital HIV infection, but the majority of congenital infections occur with intrapartum transmission and direct exposure to maternal secretions and blood. Ex vivo, chorionic villous explants isolated from both first trimester and full-term placentae support HIV infection, suggesting the possibility that the placenta could be infected during pregnancy. However, although HIV proteins and/or nucleic acids can be detected in placental tissue collected from HIV-positive women, this occurs relatively infrequently, with studies demonstrating that the majority of placentae collected from HIV-positive women are negative for HIV.

These data concur with epidemiological data that suggest that, although transplacental transmission of HIV is possible, it is an infrequent (<1%) occurrence. However, maternal co-infection with other pathogens such as CMV or malaria may further increase the risk of vertical transmission and/or adverse outcomes.

**Zika virus.** ZIKV is a positive-strand RNA virus in the *Flaviviridae* family that caused a large outbreak of >2,000 cases of congenital disease in 2015–2016, with an epicentre in Brazil. ZIKV is transmitted through vector-dependent (*Aedes* aegypti mosquitoes) and vector-independent (for example, sexual, blood transmission and vertical transmission) routes. Maternal ZIKV infections are associated with a range of fetal clinical outcomes including ventriculomegaly, microcephaly and developmental delays, which occur in ~10% of maternally infected patients. The discrepancy between fetal infection and the diverse neurological sequelae of disease has led to the separation of congenital ZIKV infection and congenital ZIKV syndrome. Since the initial outbreak, cases of ZIKV congenital disease have waned considerably, suggesting that pre-existing immunity is important for regulating ZIKV infection of the maternal host. ZIKV infection in human placental explants and mouse models suggests clear gestational age differences in transmission efficacy and fetal sequelae, with infection in the first trimester posing the greatest risk. Interestingly, twin discordance for placental and neonatal infections has been demonstrated with up to 50% discordance in twin pairs, and this susceptibility can be recapitulated in vitro after delivery, suggesting that fetally or placentally derived factors are important for limiting vertical transmission.

Like other TORCH pathogens, the mechanisms by which ZIKV crosses the placental barrier remain largely unknown (FIG. 4), despite considerable investigation. Some studies have associated placental cell tropism of ZIKV infection with receptor expression, but receptors that are important in flavivirus binding (for example, the TAM family of receptors) are not important for ZIKV infection in vivo. In vitro mouse and ex vivo human studies have also suggested that pre-existing antibodies to the related flavivirus dengue virus (DENV), which is co-endemic with ZIKV, enhances ZIKV congenital infection and facilitates viral traversal across the placenta. However, data from human studies in endemic regions suggest that pre-existing DENV immunity is associated with reduced risk of ZIKV infection and facilitates viral traversal across the placenta. Non-human primate models of ZIKV vertical transmission have provided important insights into the complex nature of maternal–fetal infections with this virus (reviewed in Ref. 158) and have also enabled studies that investigate neonatal and infant sequelae. Even these models have yet to elucidate the precise mechanisms by which the virus traverses the placental barrier. Both animal and in vitro models highlight the multifactorial complexity of vertical transmission of ZIKV and suggest that modelling this phenomenon may be difficult.
which gyration of the brain development delay in associated with severe brain malformation (lissencephaly) treatment. parenchyma and requiring abnormality from pathological Central nervous system Hydrocephalus

Emerging viruses. Several emerging viruses may have major impacts on the mother and fetus during pregnancy. Although pregnancy is often not well studied in the setting of emerging pandemics, there are data indicating increased severity of maternal infection with Ebola virus (EBOV) and reports of vertical transmission of Rift Valley fever virus (RVFV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), West Nile virus (WNV) and Eastern equine encephalitis virus (EEEV).

EBOV belongs to the Filoviridae family, which are negative-strand, enveloped RNA viruses. EBOV infections are associated with maternal haemorrhage, preterm labour, miscarriage and maternal and fetal death. Maternal death occurs in 85% of cases with near 100% loss of offspring (stillbirth, miscarriage and neonatal death)\textsuperscript{156}. In addition to causing severe maternal disease, there are also reports suggesting vertical transmission of EBOV. During the 2013–2016 outbreak in West Africa, pregnant women were noted to survive EBOV disease even with clear viraemia, but delivered stillborn infants with elevated viral RNA levels in placental and fetal swabs, suggesting vertical transmission of EBOV\textsuperscript{155,156}. In addition, EBOV antigen has been found in the STB by immunohistochemistry, although this localization alone is insufficient to demonstrate vertical transmission and may instead suggest that the STB successfully restricted access to fetal blood\textsuperscript{159}.

RVFV is an arbovirus in the Bunyaviridae family that is transmitted through an arthropod vector and is associated with severe disease in domesticated animals and livestock. In herds, RVFV outbreaks are associated with ‘abortion storms’, in which fetal loss and/or stillbirth are observed in as many as 90–100% of pregnant animals. A single case study has demonstrated vertical transmission in the third trimester in humans, and increased miscarriage and fetal demise in association with RVFV has also been described\textsuperscript{161,162}. In human placental tissue ex vivo, viral replication has been demonstrated in both the STB and in CTBs\textsuperscript{163,164}, but the specific route of vertical transmission in livestock and in humans, and whether these routes are similar, remains unclear.

WNV is an arthropod-borne flavivirus associated with marked neurotropic pathology. There have been several case reports of vertical transmission in humans, and a case series demonstrated an association with central nervous system abnormalities (hydrocephalus, microencephaly and lissencephaly)\textsuperscript{165}, but larger case studies are needed to confirm the association, and the frequency of vertical transmission remains unknown. In mouse models, WNV induces ZIKV-like fetal death and disease, suggesting a potential to cause congenital disease in vivo\textsuperscript{157}. In addition, human placental tissue including decidua, chorionic villi and fetal membrane samples are permissive to varying degrees\textsuperscript{166}. In placental villi, EVTs are preferentially infected\textsuperscript{155} and the STB remains largely resistant to infection\textsuperscript{166,167}, similar to what is described for ZIKV infection. Similar findings with Powassan virus (POWV) suggest that some emerging neurotropic arboviruses have the potential to affect fetal development if vertically transmitted\textsuperscript{168}. By contrast, other arboviruses including chikungunya virus (CHIKV) and Mayaro virus (MATV) did not cause fetal disease in mice and replicated inefficiently in human placental explants, suggesting differences in the teratogenic potential of emerging arboviruses\textsuperscript{158}.

Most recently, the SARS-CoV-2 pandemic has highlighted the need to focus on women’s health, particularly during pregnancy. Several case reports from COVID-19-positive pregnant women describe infection of the STB by immunohistochemistry accompanied by placental pathological lesions\textsuperscript{168,169}. Importantly, the vast majority of cases do not demonstrate any evidence of vertical transmission\textsuperscript{170–173}, suggesting that the placenta retains its barrier function even in the setting of severe maternal infection and disease. Thus, despite the magnitude of the pandemic, the risk to the fetus as a result of vertical transmission of SARS-CoV-2 appears to be minimal and there are no data to suggest that SARS-CoV-2 is in any way teratogenic itself.

Parasites

There are several relevant parasitic infections in pregnancy that cause fetal disease globally. These parasites differ in the mode of transmission to the maternal host,
but all have substantial implications for global maternal and child health.

**Toxoplasma gondii.** There are more than 200,000 cases of congenital toxoplasmosis globally each year\(^\text{174}\). *T. gondii* infects ~6–70% of fetuses, with maternal infection depending on gestational age at infection, and can be associated with devastating consequences, including ventriculomegaly, intracranial calcifications, chorioretinitis and rarely hydrocephaly\(^\text{174–176}\). Maternal symptoms occur in only ~5% of cases and clinical sequelae are thus best characterized in studies in which routine antenatal screening is performed, as maternal infection is subclinical. Fetuses infected early in pregnancy are far more likely to display clinical disease. Only 9% of women with seroconversion at the end of pregnancy deliver children with neurodevelopmental delays (in comparison with 25% of those with seroconversion in the second trimester)\(^\text{177}\).

*T. gondii* infection has been extensively studied at the cellular and molecular level in many non-placental cells. Infection is a multistep process that includes adhesion between *T. gondii* surface molecules and host cell surface proteoglycans, attachment that is driven by secretion of proteins into the host plasma membrane and invasion into the host cell that is mediated by interactions between parasite surface proteins and parasite proteins secreted onto the cell surface (reviewed in Refs\(^\text{178,179}\)). *T. gondii* also secretes protein effectors into the host cell during infection (reviewed in Refs\(^\text{186,187}\)). These diverse effectors alter many fundamental aspects of host cell biology, including innate immune pathways that are important for defensive signalling\(^\text{188}\). Despite characterization in non-placental cells, the mechanisms of *T. gondii* vertical transmission remain unclear. The STB displays distinct resistance to *T. gondii* infection, which occurs at the level of attachment and post-entry replication\(^\text{188,189}\). By contrast, CTBs and EVTs do not display the same degree of resistance\(^\text{188,189}\), suggesting cell-type specific differences in mechanisms of resistance. In addition to cell-intrinsic defences, trophoblasts also respond to *T. gondii* infection through the specific induction of various cytokines and chemokines, including the robust induction of the regulatory T cell chemokine CCL22 (Ref\(^\text{189}\)). Remarkably, this induction is not driven by trophoblast sensing, but instead requires the delivery of the *T. gondii*-derived effector molecular GRA28 (Ref\(^\text{23,182}\)). However, it remains unclear what role placenta-derived cytokines or chemokines have in *T. gondii* pathogenesis and vertical transmission.

**Plasmodium species.** Of the four malarial species that cause disease in humans, *Plasmodium falciparum* causes the majority of disease in pregnancy. In areas of low transmission and low pre-existing immunity, congenital infection is symptomatic and causes cerebral malaria, respiratory distress syndrome, refractory hypoglycaemia, and miscarriage and stillbirth. In areas where the parasite is endemic and pre-existing immunity is high, malaria can cause severe maternal anaemia, preterm delivery and fetal growth restriction, and remains a major cause of neonatal mortality\(^\text{190–192}\). Congenital infection has been reported, and data suggest that perinatal acquisition through vertical transmission also occurs in endemic areas\(^\text{193–195}\).

The *Plasmodium* parasite has a clear predilection for the placenta. Attachment of infected erythrocytes to the placenta allows the parasite to evade the maternal immune response by changing surface antigens (described in detail below), and histopathological specimens from pathogenic malarial infection contain a substantial number of erythrocytes in the intervillous space with parasites and acute and chronic intervillositis\(^\text{196,197}\). Owing to placental malarial burden, nutrient transport across the placenta is reduced, which highlights how placental function can be compromised by infection\(^\text{196,192}\) (FIG. 5).

The mechanisms for placenta-specific binding and sequestration of infected erythrocytes have been relatively well characterized. *Plasmodium*-infected erythrocytes bind to endothelial receptors for tissue sequestration in non-placental tissues through parasite-encoded variant surface antigens (VSAs) that are expressed by the infected erythrocyte (reviewed in Ref\(^\text{198}\)). Expression of the VSA gene family *var* varies over the course of an infection. *var* encodes ~60 erythrocyte surface proteins annotated *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), which are responsible for adhesion to uninfected erythrocytes and other cell types\(^\text{199–199}\). During the course of infection, antigenic variation in expression of different family members in the gene family *var* occurs, allowing immune evasion. During pregnancy, the parasite adapts to the presence of the placenta, allowing placental sequestration and immune evasion as well as maternal and fetal disease (FIG. 5). The *Plasmodium* gene encoding VSA 2CSA (var2csa) is selectively transcribed in placent al malaria and allows the infected erythrocyte to adhere to the STB\(^\text{200,201}\). Outside of pregnancy, CD36 is a major receptor for infected erythrocytes, but chondroitin sulfate A (CSA) on the STB becomes the major receptor for VAR2CSA and is important for placental sequestration\(^\text{202–204}\). The upregulation of VARCS2A by the parasite in infected erythrocytes during pregnancy allows evasion of a pre-existing immune response in endemic areas and explains how primigravidity (that is, being pregnant for the first time) is a risk factor for severe disease. Accordingly, antibodies to placenta-specific VSAs including VAR2CSA are not present in men and do not develop until later in pregnancy\(^\text{201–203}\). VSAs are primary targets for maternal IgG, and elevated levels and a higher affinity for VSAs are protective from severe disease\(^\text{204–206}\). Placental sequestration of infected erythrocytes leads to an influx of phagocytes and cytokines, which is thought to damage the adjacent STB and lead to adverse outcomes in the absence of fetal parasitaemia\(^\text{194,207,208}\) (FIG. 5).

Recently, placental autophagy, a mechanism to maintain normal cellular homeostasis, has been demonstrated to be dysregulated in placental malaria infection, which leads to decreased amino acid transport to the fetus and has been implicated in the development of fetal growth restriction\(^\text{209,210}\).

**Trypanosoma cruzi.** Chagas disease is caused by infection of *T. cruzi*, typically from an arthropod vector. Most women of reproductive age in endemic areas are
infected and ~5% transmit the parasite vertically\textsuperscript{211}. Most congenitally infected infants are asymptomatic but can develop life-threatening and disabling disease later in life. Features of symptomatic congenital Chagas disease include a low Apgar score\textsuperscript{2}, neonates that are small for gestational age and signs of liver failure and hydrops\textsuperscript{212,213}. Different strains of \textit{T. cruzi} demonstrate differential tropism for placental tissue, although the mechanistic basis for this remains unknown. High maternal parasitaemia correlates with congenital transmission\textsuperscript{214,215}. Despite the fact that placental pathology demonstrates a predilection of the parasite for the decidua, ex vivo placental explants demonstrated that the parasite interacts with the STB and causes local destruction and detachment, likely through apoptosis\textsuperscript{216,217}. Interestingly, \textit{T. cruzi}-derived exosomes, a marker of increased parasitic burden and severe disease, cause inflammation and histopathological damage to the STB in placental explants\textsuperscript{218}, suggesting that these exosomes may lead to inflammation-mediated damage and allow the parasite to cross the syncytiotrophoblast barrier. The parasitic mechanisms responsible for tissue damage are an area of ongoing investigation, but it is thought that after the trypomastigote gains access to the intervillous extracellular matrix, its degradation promotes parasite access to the fetal circulation\textsuperscript{216}.

Conclusions
There are substantial consequences resulting from infections in pregnancy. The complexity and unique features of the maternal–fetal interface have led to the discovery of multiple pathways of host–pathogen interactions unique to this niche. Yet, the molecular mechanisms of pathogenesis remain largely uncharacterized, in part owing to the complexities of defining the interactions that occur between the pathogen and maternal and/or fetal hosts during the context of pregnancy. Moreover, modelling the unique tissue architecture and immunology of the maternal–fetal interface creates additional complexities in delineating microbial vertical transmission strategies. Although the use of mouse models has provided important insights into various aspects of pregnancy, there are substantial differences in the placental architecture between human and mouse (reviewed in Refs\textsuperscript{16,219}) that limit direct correlates of these findings to humans. Although the placentae of primates and guinea pigs have a more similar architecture to that of humans, these models can be difficult to establish, and their lack of genetic tractability limits some mechanistic studies. Lastly, both clinical samples and primary tissues provide human-based models to study pathogenic mechanisms or vertical transmission of TORCH pathogens; however, there can be limited access to healthy placentae to generate these models. Recently, the development of stem cell-derived organoid models of both maternal and fetal cell types\textsuperscript{220,221} at the maternal–fetal interface has opened up exciting new avenues to model this interface. However, organoid models lack immune cell components and do not recapitulate the immunological crosstalk that undoubtedly alters antimicrobial defences. The fetal and maternal immune cell phenotypes at the maternal–fetal interface are still an area of active investigation and characterization. Further understanding

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Apgar score
A score assigned to neonates associated with neonatal health after birth. Infants are scored 0–2 points on muscle tone, skin colour, respiratory effort, pulse and reflex irritability at 1, 5 and 10 min after birth.
of the contribution of the immune cell populations enriched at the interface will be essential to further define mechanisms of pathogenesis in pregnancy.

Future studies elucidating the complexity of interactions between maternal and fetal tissues and how these interactions are modulated by pathogens are crucial to the development of targeted therapeutics. Moreover, understanding the mechanisms of microbial pathogenesis across the maternal–fetal interface has broader implications in the study of infertility, miscarriage and hypertensive disorders of pregnancy and parturition, which may share common aetiology. Although the complexity of pregnancy and the current gaps in understanding of many of the fundamental aspects of infections at the maternal–fetal interface represent a challenge, further investigation into this crucial aspect of human health will lead to strategies that could substantially improve maternal and child health.

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