Comprehensive analysis of COVID-19 during pregnancy

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ABSTRACT

The COVID-19 pandemic resulting from the emergence of the coronavirus SARS-CoV-2 remains a major global health concern. Pregnant individuals are more likely to develop severe COVID-19 and a number of pregnancy complications have been observed in COVID-19 patients. To date, little is known about the impact of COVID-19 on pregnancy. In this review, we examine key aspects of pregnancy that may be impacted by COVID-19 and summarize the current literature on SARS-CoV-2 infection of the placenta and *in utero* vertical transmission. Furthermore, we highlight recent studies exploring the role of the maternal antibody response to SARS-CoV-2 during pregnancy and the passive transfer of maternal antibodies from mothers with COVID-19 to fetus.

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1. Introduction

The coronavirus disease 19 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single stranded positive sense RNA virus belonging to the family of coronavirus. To date, the global number of COVID-19 cases reported by Johns Hopkins University is 74.3 million people and over 1.6 million people have died [1]. The primary route of transmission is through respiratory droplets, whereby infection seeds the respiratory tract [2]. COVID-19 manifests mainly as a pulmonary disease, and presents with flu-like symptoms include fever, cough, shortness of breath, fatigue, and headache. The breadth of SARS-CoV-2 infection severity ranges from no symptoms to critical illness that can result in pneumonia and respiratory failure [2]. Several risk factors for severe COVID-19 disease have been identified, including age ($\geq$50 years old), male sex, and comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease [3].

SARS-CoV-2 infection within the lungs can lead to damage to type I and II pneumocytes, inflammation and hemorrhage [4,5]. The resulting vascular leakage could provide a mechanism for SARS-

CoV-2 to gain access to other organs by dissemination through the bloodstream [6]. Indeed, SARS-CoV-2 RNA has been detected in the plasma of patients, yet infectious virus has not yet been cultured from the blood [7,8]. Regardless, COVID-19 patients have demonstrated extrapulmonary manifestations including neurologic, renal, hepatic, gastrointestinal, thromboembolism, cardiac, endocrine, and dermatological symptoms [9]. Many tissues appear to be susceptible to SARS-CoV-2 cellular entry corresponding to the expression patterns of the ACE2 receptor [10]. Further examination is warranted to determine the extent of SARS-CoV-2 extrapulmonary infection in patients across the disease spectrum. There are possible mechanisms for these extrapulmonary symptoms other than direct injury from viral replication. For example, some have proposed that endothelial cell damage mediated by inflammation may be responsible for promoting coagulation, resulting in formation of the microthrombi that are found in the extrapulmonary organs of some severe COVID-19 patients [11]. COVID-19 can also cause immune dysregulation, and severe cases are associated with over-production of pro-inflammatory cytokines [12].

1.1. COVID-19 and pregnancy

According to the Centers for Disease Control and Prevention (CDC), there have been around 49,000 cases of pregnant women with COVID-19 in the US to date [13]. Little is known about the impact of pregnancy on COVID-19 and vice versa. Pregnant women with COVID-19 are more likely to develop severe illness than non-

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pregnant women, with an increased rate of admission to the intensive care unit, need for supplemental oxygen, ventilation, and mortality [14]. In a recent meta-analysis, Dubey et al. found that 27% of pregnant individuals with COVID-19 had adverse pregnancy events such as preterm birth, fetal vascular malperfusion, and premature fetal membrane rupture [15]. The CDC conducted a surveillance analysis encompassing 598 pregnant individuals with laboratory confirmed COVID-19 from March to August 2020 and found that 12.6% of the births were preterm (<37 weeks) [16]. This is higher than the preterm birth rate observed in the US, which was around 10% in 2018. Furthermore, they estimated that preterm birth was three times more frequent in symptomatic mothers compared to those with asymptomatic COVID-19 [16]. A higher incidence of fetal vascular malperfusion have been observed in COVID-19 pregnancies, which encompasses thrombosis, poor development of vasculature, and fibrin deposition within the fetal vasculature located within the placenta [17]. An increase in premature rupture of the fetal membrane has also been reported, which can lead to preterm birth [18,19]. Some of these pregnancy complications observed may be attributed to the extrapulmonary pathology of COVID-19. Pregnancy enhances the risk of thromboembolic complications due to the increased levels of coagulation factors in the blood [20]. Increased D-dimer concentration in COVID-19 patients, indicating degradation of a blood clot, correlates with poorer outcomes [3]. COVID-19 may further enhance hypercoagulability in pregnant individuals, putting them at even greater risk for thromboembolism [20].

Pre-eclampsia, a pregnancy complication that occurs in around 6–8% of pregnancies, has several overlapping features with COVID-19, including high blood pressure, thrombocytopenia (i.e. low platelet count), and immune dysregulation [21,22]. Both hypertension and thrombocytopenia are strong predictors of morbidity and mortality in COVID-19 patients [3,23]. In an observational study, pregnant individuals with severe COVID-19 were found to have pre-eclampsia-like symptoms but did not have elevated levels for other pre-eclampsia markers (fms-like tyrosine kinase-1 and placental growth factor), suggesting that COVID-19 induced systemic inflammation may lead to similar clinical manifestations as pre-eclampsia without the characteristic abnormal placentation [24,25].

Maternal serum pro-inflammatory and anti-inflammatory cytokine levels are tightly regulated during pregnancy. The first trimester of pregnancy is skewed towards a pro-inflammatory state, whereas the last two trimesters are anti-inflammatory. Systemic pro-inflammatory cytokines such as CXCL10, TNF-α, IL-18, IL-6, CXCL8 remain steady over the last two trimesters of pregnancy, while anti-inflammatory cytokine levels increase over time, shifting the balance away from the initial pro-inflammatory state [26]. High levels of IL-6 in the blood, indicating systemic inflammation, is characteristic of severe COVID-19 and correlates with respiratory failure [27]. As seen in pre-eclampsia, disruption of immune regulation that results in systemic inflammation puts the pregnancy at risk for fetal demise and maternal death. Notably, IL-6 is also a marker associated with pre-eclampsia and has been proposed as a mediator for pre-eclampsia pathogenesis [22]. Interestingly, Zeng et al. detected elevated levels of IL-6 in the serum of neonates from mothers with mild COVID-19 at the time of birth [28]. However, Sherer et al. reported no difference in maternal serum IL-6 between healthy pregnant individuals and those with mild to moderate COVID-19 in a recent pre-print [29]. In light of the association between systemic inflammation and pregnancy complications, there is a need for further examination of the impact of SARS-CoV-2 induced cytokines on pathogenesis over the course of pregnancy.

1.2. Evidence for SARS-CoV-2 infection of the placenta

The developing fetus can be impacted directly by viral infection as a result of vertical transmission (i.e. transmission from mother to fetus) or indirectly by viral infection of the placenta. The placenta forms a physical and immunological barrier between mother and fetus, serving to protect the developing fetus from infection and maternal rejection, while facilitating the exchange of nutrients and waste. The fetal vasculature resides within the chorionic villi, surrounded by a layer of mononucleated cytotrophoblasts followed by multinucleated syncytiotrophoblasts. The chorionic villi are either floating in maternal blood or are anchored to the basal decidua along the uterine wall. The stroma of the chorionic villi also contains fibroblasts and macrophages known as Hofbauer cells.

There are a variety of innate immune mechanisms at the maternal-fetal interface that protect the fetus [30,31]. Around 30% of the cells that reside in the decidua are immune cells, a large proportion of which are natural killer cells [32,33]. Syncytiotrophoblasts, which form the outermost layer of the chorionic villi and are in direct contact with the maternal blood, secrete antimicrobial molecules, cytokines, and microRNAs that restrict pathogen infection [30,34]. A hallmark of the placental antiviral defense is high levels of the type III interferon, IFN-λ, secreted by syncytiotrophoblasts [31,35,36]. Interestingly, treatment with IFN-λ has been shown to restrict SARS-CoV-2 infection in primary human airway epithelial cultures [37]. Future experimental studies are needed to determine if the placenta is permissive to SARS-CoV-2 replication, but if so, it raises the question of how it may bypass the innate immune response within the placenta.

Evidence of SARS-CoV-2 presence in the human placenta has been observed through a number of different laboratory techniques, such as PCR [38–40], positive strand RNA in situ hybridization [39,41,42], immunohistochemistry [38,39,43,44], and transmission electron microscopy [39,45]. Primarily, these observations have been made in the syncytiotrophoblast layer of the chorionic villi [39,41,42,46]. To our knowledge, negative sense RNA has not yet been detected in the placenta, which would indicate viral replication since it is a replicative intermediate of positive sense RNA viruses, such as SARS-CoV-2. It is unclear at this time how these viral antigens or particles gained access to the placenta and if infection is established within the placenta.

There have been several studies investigating the susceptibility of the placenta for SARS-CoV-2 infection by evaluating expression of key cellular machinery for SARS-CoV-2 entry using publicly available single cell RNA sequencing data [46–48]. For SARS-CoV-2, human angiotensin-converting enzyme 2 (ACE2) has been identified as the canonical receptor for cellular entry. In addition, co-expression of the protease, TMPRSS2, is required to cleave the spike (S) protein on SARS-CoV-2, mediating ACE2 binding [49]. Low levels of ACE2 and TMPRSS2 mRNA have been detected in syncytiotrophoblasts and extravillous trophoblasts [46,47]. Furthermore, ACE2 and TMPRSS2 antigens have both been identified in the syncytiotrophoblast and cytotrophoblast layers of the chorionic villi by immunohistochemistry [41,43]. In comparison to receptors for viruses that are known to infect the placenta, such as Zika virus (ZIKV) and cytomegalovirus (CMV), expression of ACE2 and TMPRSS2 was substantially lower [48]. It is important to point out that neither SARS-CoV-2 cellular entry via ACE2 binding, nor replication within placental cells has been demonstrated experimentally.

Susceptibility for SARS-CoV-2 infection of the placenta may also be influenced by complications such as placental inflammation. In a pre-print, Lye et al. reported that ACE2 expression was increased in placentas that experienced inflammation as a result of intrauterine bacterial infection, known as chorioamnionitis [50]. Treatment of

Table 1

Summary of case reports detailing confirmed or possible instances of SARS-CoV-2 vertical transmission. Sample sizes of n = 1 unless otherwise noted. Tests are recorded as positive (+) or negative (−) followed by the day that the sample was taken in parentheses (DX), where X = number of days post-delivery. NSP: nasopharyngeal swab.

	Mother		Neonate		
Ref	SARS-CoV-2 PCR Test	Placenta Histology	SARS-CoV-2 PCR Test	IgM Antibodies	Other
[28]	NSP: + (D0), (n = 6/6)	–	Throat: (D0), (n = 0/6) Serum: (D0), (n = 0/6)	Serum: + (D0), (n = 2/6)	Elevated serum IL-6 (D0), (n = 6/6)
[59]	NSP: + (D0)	–	NSP: + (D0, 2)	Serum: (D0, 4, 5)	Ventilation for 12 h after birth; Mild respiratory symptoms (D6)
[56]	NSP: + (D-12, -3, 8)	–	NSP: (D2, 5, 8, 13, 14, 16)	Serum: + (D0)	Elevated serum IL-6 and IL-10
[57]	NSP: + (D-1)	Inflammation	NSP: + (D0, 2, 7) Serum: + (D4) Stool: + (D7)	–	–
[55]	NSP: + (D-3)	–	Amniotic fluid: + (D0) Umbilical cord blood: (D0) NSP: (D0), + (D1)	–	–
[39]	NSP: + (D0) Placenta: + (D0)	Inflammation; SARS-CoV-2 RNA and protein	Umbilical cord: + (D0)	–	–
[38]	NSP: + (D0) Serum: + (D0) Placenta: + (D0) Vaginal: + (D0)	Inflammation; SARS-CoV-2 protein	Amniotic fluid: + (D0) Serum: + (D0) NSP: + (D0, 2, 17) Rectal: + (D0)	–	MRI: Brain white matter injury (D11); Reduced injury at 2 months
[58]	NSP: + (D0), (n = 30/31) Serum: + (D0), (n = 1/30) Placenta: + (D0), (n = 2/31) Vaginal: + (D0), (n = 1/30)	–	Umbilical cord blood: + (D0) (n = 1/31) NSP: + (n = 2/31)	Umbilical cord blood: + (D0), (n = 1/31)	Elevated serum IL-8, CCL2, CCL3, CCL5, CXCL10 (D0), (n = 2/31)

placental explants with LPS resulted in enhanced ACE2 expression *ex vivo*. In light of these findings, the authors proposed the possibility of vertical transmission by way of SARS-CoV-2 carrying immune cells infiltrating placentas complicated with chorioamnionitis. Chorioamnionitis has been observed upon histological analysis of placentas from pregnant individuals with COVID-19 in the absence of premature rupture of the fetal membrane or other acute infections [51,52]. Yet, others have found that rates of placental inflammation do not differ between patients with COVID-19 and healthy controls [41,53]. Larger studies are needed to resolve the rate of this complication and its association with gestational age and disease severity.

1.3. Evidence for SARS-CoV-2 vertical transmission in utero

Many case reports have been published detailing evidence for and against SARS-CoV-2 vertical transmission. We define vertical transmission as the transmission of pathogens from mother to fetus *in utero*. Shah et al. makes an argument for a classification system for likelihood of SARS-CoV-2 congenital infection (i.e. vertical transmission, by our terminology) based on standards for confirming other congenital infections such as Toxoplasma gondii, in which cases are outlined as "confirmed," "probable," "possible," "unlikely," and "not infected" based on defined criteria [54]. There are several noteworthy case reports that would be considered "confirmed" or "possible" cases of vertical transmission, which we have highlighted in Table 1 [28,38,39,54–58]. Confirmed cases must demonstrate a positive PCR test from amniotic fluid, umbilical cord blood, or neonatal blood within the first 12 h after birth. SARS-CoV-2 mRNA has indeed been detected by PCR in the amniotic fluid prior to membrane tearing during cesarian section delivery [38,55], in the umbilical cord [39,58], and in neonatal serum upon delivery [38]. Zamaniyan et al. and Hosier et al. reported cases in which a neonate tested PCR positive from a nasopharyngeal swab upon delivery but with no placental swab or any other confirmatory test that day, and as such are considered possible cases [57,59]. Zeng et al. and Dong et al. detected IgM in the serum of neonates at birth

but with negative nasopharyngeal swabs [28,56]. Since IgM cannot cross the placenta and usually takes several days to be produced, presence of IgM in the umbilical cord blood or neonate shortly after birth suggests that the neonate was possibly exposed to the virus *in utero* and generated their own IgM. However, evidence of SARS-CoV-2 presence in the fetal compartment is needed to confirm this possible case.

Several studies have reported elevated inflammatory cytokines in the serum of neonates upon delivery. In Fenizia et al. the two neonates, out of 31 from COIVD-19 positive mothers, that tested positive for SARS-CoV-2 by PCR of nasopharyngeal swab also had elevated serum cytokines. However, since the only other two samples tested were neonatal serum from a mother recovered from COVID-19 and an unexposed individual, further studies are needed to conclude that the inflammatory cytokines are indicative of maternal or neonatal infection. It is also important to note that IL-6 has previously been shown to impact the brain of the developing fetus in studies predating the COVID-19 pandemic [60]. This syndrome is referred to as maternal immune activation and is associated with neurodevelopmental disorders. The cognitive function in offspring of mothers that experience severe COVID-19 during pregnancy should be evaluated in future studies.

Several meta-analyses of case reports with small cohort sizes have been performed in order to gain clarity on the overall incidence of SARS-CoV-2 vertical transmission, estimating rates ranging from 3 to 8% [19,61,62]. However, the criteria for vertical transmission in theses analyses were not as strict as proposed in Shah et al. The determinant for vertical transmission in these meta-analyses was detection of SARS-CoV-2 mRNA in the neonate at the time of delivery or within 48 h after birth by PCR, which could allow for inclusion of transmission during delivery [54]. With narrower criteria, the vertical transmission rate becomes less clear due to much smaller sample sizes. Larger studies incorporating multiple types of tests for neonatal infection and characterization of maternal condition would provide more a convincing view of the rate of SARS-CoV-2 vertical transmission.

2. Maternal antibody response to SARS-CoV-2

Neutralizing antibodies have been shown to be important players in the immune response against COVID-19. The primary antigen involved in antibody-mediated neutralization is the S protein of SARS-CoV-2. SARS-CoV-2 S protein specific IgM titers in serum have been shown to peak around 14 days after symptom onset and then diminish thereafter. Conversely, IgG titers peak around 21—28 days and are usually maintained for several weeks after COVID-19 symptom onset [63—66]. The receptor-binding domain (RBD) is the structural element of the S protein that binds to the ACE2 receptor on cells. The RBD is a major target of neutralizing antibodies and anti-RBD antibody titers have been shown to correlate with SARS-CoV-2 neutralizing antibody titers [67—69]. Neutralizing antibodies are generated relative quickly; Suthar et el. found that neutralizing antibodies can be detected in the majority of individuals acutely infected with SARS-CoV-2 around 8 days after symptom onset [67]. Monoclonal antibodies against the S protein are now being used therapeutically as anti-virals in patients [70] and vaccine candidates have been shown to generate antibodies directed against S [71].

In a recent pre-print, Sherer et al. reported that pregnant individuals with COVID-19 generated the same level of anti-S protein IgG but lower levels of anti-RBD IgG compared to individuals that were not pregnant [29]. Pregnant individuals with COVID-19 were less likely to have detectable neutralizing antibodies against SARS-CoV-2 than those that were not pregnant, suggesting that the quality of the antibody response against SARS-CoV-2 during pregnancy was inferior. In light of these results, investigation into the level of protection afforded to pregnant individuals by SARS-CoV-2 vaccine candidates is needed.

2.1. Passive immunity and COVID-19

Starting around 10—12 weeks of gestation, maternal IgG is transferred across the placenta to the developing fetus to protect them from infection as a neonate. This process is called passive immunization and peaks in the last trimester, where the majority of IgG is transferred in the final 4 weeks of gestation [72—74]. Neonatal Fc receptors (FcRn) located on syncytiotrophoblasts bind to maternal IgG and facilitate their transport into the chorionic villi. IgG specific for the SARS-CoV-2 S protein has been detected in neonates in the absence of IgM or a PCR positive nasopharyngeal swab, indicating that they received the IgG passively from the exposed mother [28,75,76].

The transfer of specific maternal IgG to the fetus is influenced by several factors including level of maternal IgG and gestational age [73]. Flannery et al. reported that umbilical cord levels of SARS-CoV-2 IgG specific for the RBD increased linearly with maternal levels in a recent pre-print [76]. In this pre-print, the titers of IgG against the SARS-CoV-2 RBD increased with increasing maternal disease severity in both maternal and umbilical cord blood. The severity of COVID-19 in mothers did not have an impact on the transfer ratio of IgG, which is the ratio of total infant IgG to maternal IgG derived from cord and maternal blood, respectively [76,77]. Neonates of mothers infected with SARS-CoV-2 14 days or more prior to delivery were more likely to have seroconverted and even have a higher IgG titer at the time of delivery [76,77], which is likely a result of increased time for maternal IgG production. Sherer et al. reported that while the level of SARS-CoV-2 S protein IgG was the same in maternal serum compared to umbilical cord blood, the level of neutralizing antibodies was reduced in the umbilical cord blood [29]. However, both the expression of FcRn in the placenta and the transfer of anti-tetanus IgG in pregnant individuals with and without COVID-19 was the same. These results suggest that the

process of passive immunization from mother to fetus is not broadly hindered by SARS-CoV-2 infection [29], which is seen with placental malaria and HIV [78,79]. IgG subclass and post-translational modification such as Fc glycosylation have also been suggested to influence the transfer ratio of different antibodies [79—81]. Further characterization of the nature of anti-SARS-CoV-2 antibodies developed in pregnant individuals compared to non-pregnant may shed light on these findings.

The durability of SARS-CoV-2 specific IgG passively transferred during pregnancy remains unclear. Xie et al. reported that in the absence of breast feeding, maternal SARS-CoV-2 specific IgG in infants declined 10-fold over the first two months after delivery [77]. Gao et al. also reported SARS-CoV-2 specific IgG titers approach baseline over a similar timeframe but did not account for breastfeeding [82]. Unfortunately, neither study measured non-SARS-CoV-2 specific IgG as a control. The persistence of other maternal antibodies in infants has been shown to vary between 2 and 12 months and is influenced by antibody specificity, whether the antibodies were induced by maternal infection or vaccination, and the timing of maternal exposure to the antigen [83—86]. Future studies that examine the persistence of vaccine and infection-induced SARS-CoV-2 reactive antibodies in infants after birth and their effectiveness in protection from COVID-19 are warranted. Furthermore, studies involving the optimal immunization schedule for protection of both the mother against COVID-19 during pregnancy and the infant after delivery should be done.

2.2. Potential role of antibody mediated enhancement of SARS-CoV-2 vertical transmission

SARS-CoV-2 has been shown to enter cells by binding to ACE2. However, alternative mechanisms of cellular entry may exist and have been proposed in recently published SARS-CoV-2 literature. Antibody dependent enhancement (ADE) has been proposed as one such alternative mechanism, whereby cellular entry is facilitated by Fc receptors. ADE has been seen in cats with feline infectious peritonitis virus (FIPV) infection. Antibodies generated by FIPV immunization have been shown to enhance disease severity in cats when infected with a similar strain [87]. In this case, ADE is associated with increased infection of monocytes/macrophages as a result of antibody-virus immune complex utilizing Fc receptors to enter the cell [88]. Antibodies generated against the S protein have been shown to be central mediators of FIPV ADE, as evidenced by reduced survival in cats challenged with FIPV after immunization by a recombinant vaccinia virus expressing FIPV S protein [89]. Mutation of FIPV S protein at the site of cell receptor binding resulted in loss of neutralization and ADE activity by previously neutralizing monoclonal antibodies [90].

Human coronaviruses such as MERS-CoV and SARS-CoV have demonstrated ADE in vitro as well [91]. Antibody binding to MERS-CoV has been shown to induce a conformational change in the S protein, promoting proteolytic cleavage to allow for viral binding and entry into the cell via the canonical receptor, dipeptidyl peptidase 4 (DPP4) [92]. Neutralizing antibodies generated from hamsters vaccinated against the S protein from SARS-CoV, were found to facilitate entry into human B cells via FcγRII in vitro [93]. However, vaccinated hamsters were still protected from a SARS-CoV challenge in vivo and did not present with enhanced lung pathology or viral load.

Antibodies can also facilitate transport of viruses across the placenta by Fc receptor binding. Cross-reactive antibodies against dengue virus (DENV) enhanced ZIKV infection of ex vivo placental explants by FcRn uptake. This illuminated a mechanism by which presence of cross-reactive DENV antibodies may mediate trans-cytosis across the syncytiotrophoblast layer of the chorionic villi,

which are resistant to ZIKV infection in the absence of DENV antibodies [94,95]. Furthermore, expression of FcγR on Hofbauer cells found in the chorionic villi allowed them to be more permissive to ZIKV infection when complexed with DENV IgG [94]. In mice, the role of FcγR was found to be critical in DENV antibody mediated ZIKV pathogenesis [96]. Notably, to the best of our knowledge, SARS-CoV-2 infection of placental macrophages (Hofbauer cells) has only been identified in a single patient from one clinical report, suggesting that this mechanism may be rare in SARS-CoV-2 [97]. Similarly, Maidji et al. demonstrated that infection of *ex vivo* placental explants with antibody-CMV immune complexes facilitates transcytosis of the syncytiotrophoblast layer and infection of Hofbauer cells [98]. This work may help explain the clinical observation that production of low neutralizing maternal antibodies during infection is associated with vertical transmission of CMV [99].

3. Conclusion

Herein, we provided an overview of the knowledge currently available about COVID-19 during pregnancy. Evidence of SARS-CoV-2 has been detected in the placenta of COVID-19 positive mothers, yet experimental studies are needed to determine if this is indicative of infectious virus capable of replication in the placenta. Additionally, larger studies characterizing neonates born from mothers with COVID-19 would provide more clarity on the frequency of SARS-CoV-2 vertical transmission. SARS-CoV-2 specific IgG has been detected in neonates born to mothers with COVID-19. We offered suggestions for future studies involving the impact of antibodies in COVID-19 pregnancies, such as characterization of maternal antibodies transplacentally transferred and investigation into a possible role of antibody mediated vertical transmission.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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