////Title: The Antigen-specific Immune Response Against Malaria Acquired During Foetal Development

////Stand-first:

It is currently unknown at what point during development a human foetus can recognise antigens as foreign and produce an acquired immune response. The foetus is not usually exposed to pathogens but remains relatively protected in the uterus by the placenta, and contact with allergens, viral antigens, and so on, is fairly rare. Malaria, however, causes significant placental infection and inflammation. In regions where malaria is endemic, the foetus can be exposed to malaria parasites and their antigens from their infected mothers repeatedly during pregnancy. Dr Samuel Tassi Yunga and his collaborators from The University of Hawaii at Manoa in the USA, and the Biotechnology Center in Yaounde Cameroon, recently analysed the levels of antibodies against *Plasmodium falciparum* [fal-ˈsi-pə-rəm] in newborn Cameroonian babies to determine the timing of antibody response during prenatal development. Results provide both basic and clinically relevant information.

////Body text:

Malaria is a serious and potentially fatal tropical disease, spread to people through the bites of mosquitoes infected with the parasite known as *Plasmodium falciparum*. According to the World Health Organization, the estimated number of malaria deaths in 2019 was 409,000. Although the incidence rate of malaria is declining globally, unfortunately, it remains endemic in many countries around the world, including Cameroon.

Dr Samuel Tassi Yunga and his collaborators from The University of Hawaii at Manoa, USA, tested the hypothesis that the foetus can produce antibodies to malarial proteins (that is, antigens) if it is exposed to *P falciparum*. The study was conducted at the Central Maternity Hospital in Yaoundé, Cameroon's capital city. At the time of the study, individuals received an estimated one or two infective mosquito bites per month, and women were most likely infected several times with *P falciparum* during pregnancy, meaning that their foetuses could have been exposed to the parasite.

…

Dr Tassi Yunga and his team based their research on previous studies on white blood cells in samples of umbilical cord blood. Critically, those reports showed that 25 to 60% of Kenyan and Cameroonian newborns exposed to *P falciparum* antigens *in utero* secreted interferon, interleukins and other substances linked to the initiation of an immune response.

Furthermore, in areas with a high prevalence of malaria, newborns were found to have larger spleens compared to newborns in non-endemic areas. The proliferation of white blood cells in the newborn's spleen suggests that an immune response against the parasite's antigen has taken place in the womb. It remained unclear, however, at what stage of foetal development the antibodies against *P falciparum* are produced.

…

Dr Tassi Yunga's team analysed the levels of cord blood IgM antibodies against *P falciparum* antigens in 232 preterm and 450 term newborn infants. Preterm births were defined as those occurring between 20 and 36 weeks of gestation and term births were defined as those occurring after 37 weeks or more of gestation.

Existing plasma samples and clinical data were obtained from the Central Maternity Hospital for laboratory and computational analyses by the researchers. Many of the infants were born during peak malaria transmission periods in Cameroon, increasing the likelihood of their being exposed *in utero*.

Based on data from the 232 preterm babies, having a preterm baby was associated with higher placental parasite density, perhaps suggesting that maternal malaria had contributed to these early births. Around one-quarter of the 682 newborns had developed IgM antibodies against *P falciparum*, confirming that they had been exposed to the parasite in the womb. Since maternal IgM antibodies do not cross the placenta, the detection of IgM antibodies in cord blood indicated that they were produced by foetal B cells.

The earliest response detected occurred at 22 weeks and the odds of being positive for the IgM antibodies decreased with gestational age. Despite this, preterm foetuses had the same ability to produce antibodies as term foetuses. Additional in vitro studies of cord blood B cells confirmed that while the antibody response during the second trimester consisted of predominantly IgM, term foetuses predominantly made IgG against the parasitic antigens. Newborns of HIV-positive mothers were excluded.

This was the first comprehensive investigation of foetal antibody responses to malarial infection in a large sample of neonates over a broad range of gestational ages. Since human foetuses face relatively little exposure to foreign antigens in the womb, little has been known about the timing and nature of acquired immune responses during foetal development.

Despite the previously long-held belief that foetuses recognise all foreign antigens as 'self' and become tolerant to them, it is now clear that the foetal immune system is able to recognise and respond to pathogens. For example, there have been reports of a foetal inflammatory response syndrome occurring when pathogens infect the amniotic cavity. Antigen-specific T- and B-cell responses have been detected against a diverse range of pathogens, including rubella virus and hepatitis B virus.

The ability of the immune system to specifically respond to antigens is thought to depend, in part, on the diversity of T and B cell receptors. Since the range of foetal immune receptors increases with gestational age, we might be tempted to assume that preterm newborns make less antigen-specific antibodies than term newborns. However, a significant finding in this study was that both term and preterm newborns were able to produce similar levels of antibodies against a comparable breadth of *P falciparum* antigens.

In light of their findings, Dr Tassi Yunga and his team speculate that the impact of gestational age on B and T cell receptor diversity is not a limiting factor in the production of an effective antibody response against malaria *in utero*.

…

Dr Tassi Yunga and his collaborators now propose a model for the timing of foetal exposure and antibody responses to *P falciparum*. The foetus may be exposed to the parasitic antigens, from early in the second trimester, around 22 weeks, through term. In response to the antigens, both preterm (including critically preterm) and term foetuses are capable of producing antibodies that are antigen-specific. However, the antibody response during the second trimester is predominantly IgM while term foetuses predominantly make IgG.

Information on the development of the human immune response *in utero* is difficult to obtain, so this study is unique in that the researchers were able to determine that the foetus can produce an antigen-specific antibody response as early as 22 weeks of gestation and that antibody class-switching may occur early in the third trimester.

Since publishing the results of this study, Dr Tassi Yunga has continued to contribute to the fight against malaria by defining how prenatal exposure to malaria antigens contribute to susceptibility to the malaria parasite infection after birth.

P falciparum malaria is one of the top three major infectious diseases in the world today, and the findings are of importance to individuals in malaria-endemic countries. However, the results have a larger application than just malaria. Dr Tassi Yunga's work on foetal and early childhood malaria provides a blueprint for the dynamics and long-term impact of the immune responses of the foetus to allergens and antigens of other pathogens that cross the placenta. Dr Tassi Yunga has also worked on developing novel, non-invasive methods to quickly detect the presence of *P falciparum* in saliva and other easily accessible samples, methods which are applicable for non-invasive detection of other diseases, including cancer.

This SciPod is a summary of 'Timing of the human prenatal antibody response to *Plasmodium falciparum* antigens' published in the open access journal PLOS ONE.
https://doi.org/10.1371/journal.pone.0184571

You can connect with Dr Samuel Tassi Yunga at tassiyun@ohsu.edu