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Progress towards vaccines to protect pregnant women from malaria

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Pregnant women are particularly susceptible to infection with the malaria parasite *Plasmodium falciparum*, with severe consequences for maternal and offspring health. Malaria-infected erythrocytes (IEs) adhere to the syncytiotrophoblast lining the maternal blood space in the placenta, by binding to the glycosaminoglycan, chondroitin sulfate A (CSA). These placental-binding parasites express a protein that binds to CSA called VAR2CSA, a member of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family [1]. Pregnant women become protected from placental malaria over successive pregnancies, and this protection correlates with the development of antibodies to VAR2CSA which block adhesion to CSA in the placenta and opsonise IEs for clearance by phagocytic cells. Antibodies to VAR2CSA, expressed on IEs or as recombinant proteins, have been associated with protection from complications of pregnancy malaria, including low birth weight and maternal anaemia [1].

Given its central role in malaria in pregnancy, VAR2CSA is an attractive vaccine candidate, but it is a large, complex protein, composed of six Duffy binding like (DBL) domains and cysteine rich interdomain (ID) regions, and expression of the full protein is difficult. However, two overlapping but distinct constructs from its N-terminal region bind to CSA with an affinity similar to that of the full-length protein [2]. This subregion of VAR2CSA comprises variable parts of the flanking ID1 and ID2 domains, and in one case the upstream DBL1 domain. The ID1-DBL2x region has been termed the minimum binding domain (MBD). Two candidate vaccines based on these overlapping regions encompassing the MBD have been developed. PRIMVAC is derived from VAR2CSA of parasite line 3D7, and PAMVAC from the VAR2CSA of genetically distinct parasite line FCR3.

In the present issue, Chêne et al. [3] report the Good Manufacturing Practice (cGMP) manufacture and the pre-clinical evaluation of PRIMVAC, the 3D7 MBD-based vaccine candidate. The protein was potent and stable over extended storage, and when adjuvanted with either Alhydrogel or Glucopyranosyl Lipid Adjuvant-Stable Emulsion (GLA-SE) it was well tolerated and induced antibodies that recognised the homologous and two heterologous CSA-binding parasite lines. Results for adhesion inhibition were less consistent. Pools of serum made from vaccinated rats inhibited homologous parasites binding CSA (though this varied by adjuvant, time point and rat sex) and against one of two heterologous parasite lines, in female rats with Alhydrogel only. Based on these results, PRIMVAC has progressed to phase Ia/Ib clinical trials.

In parallel, early clinical results with PAMVAC were recently reported [4]. German volunteers were immunised with a protein based on the MBD of FCR3, adjuvanted with Alhydrogel, GLA-SE or GLA-LSQ (liposomal formulation with QS21) three times, four weeks apart. The vaccine was safe, well tolerated, and immunogenic. GLA-based adjuvants gave higher titres of IgG against the vaccine antigen and elicited binding inhibitory antibodies against the homologous isolate in a significant proportion of recipients. A high correlation of IgG between homologous and heterologous DBL2 domains was also observed after GLA-adjuvanted vaccination. Together these studies indicated that MBD-based vaccines are immunogenic and induce functional antibodies against homologous parasites and a level of heterologous antibody.

There is significant genetic diversity in VAR2CSA, with multiple insertions and deletions as well as SNPs in the MBD, with the greatest diversity seen in African isolates [5]. In addition, about 25% of parasite isolates have more than one VAR2CSA copy [5]. Sequences of the MBD domain can be divided into four or five phylogenetic clades [5,6]. Of these, the 3D7-like and FCR3-like clade sequences account for the majority of isolates analysed, and 3D7-like parasites have been associated with low birth weight [5,6]. Whether a VAR2CSA vaccine needs to incorporate members of multiple clades, or whether a single representative is sufficient to induce protection against isolates expressing MBDs of other clades, or even against heterologous parasites the same clade, will require further study.

Vaccines against other parasite stages could also protect pregnant women. The RTS,S vaccine protected young children against severe and uncomplicated malaria [7] and boosting existing immunity to RTS, S might protect pregnant women from malaria. A whole sporozoite based vaccine, PfSPZ, is in clinical trials, and a recent workshop discussed both regulatory and ethical issues around such a pregnancy malaria vaccine, as well as possible administration schedules [8]. These might include co-administration with HPV in adolescence, boosting during pregnancy, or even initiating vaccination early in antenatal care, although the latter may be suboptimal as early pregnancy malaria is common and dangerous for mother and baby [9] and many women attend antenatal clinic late. Any vaccine to be used in pregnant women will require extensive safety evaluation, which is complex given the high prevalence of adverse pregnancy outcomes in many settings where it might be used, rendering detection of vaccine-associated safety signals difficult. Measuring efficacy also requires careful thought, although the primary endpoint is likely to be protection against placental

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and peripheral parasitaemia. Despite the potential difficulties in implementing a vaccine to protect pregnant women, it is important that developing such a vaccine is not put in the 'too hard basket.'

These early steps in evaluating promising vaccines to minimise the scourge of malaria in pregnancy are important. From 2009 to 2012 an estimated 200,000 neonatal deaths could have been prevented just by increasing coverage of insecticide treated nets and intermittent preventive treatment to 80%, as endorsed by WHO [8]; an effective vaccine could save even more lives.

Author disclosure

Authors declare no conflicts of interest.

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