study also assessed the response to inactivated influenza vaccine and found similar seroconversion rates during the three trimesters of pregnancy (Sperling *et al.*, 2012). Finally, the ability of pregnant women to respond to recall antigens was recently demonstrated in a randomized controlled trial of tetanus–diphtheria–acellular pertussis immunization. The immunogenicity was shown to be similar in pregnant and non-pregnant women (Munoz *et al.*, 2014). In summary, B cell compartments, including naïve and memory B cells, appear poorly affected by pregnancy; response to both neo and recall antigens can be elicited during pregnancy making maternal immunization an important strategy to improve global maternal, newborn and child health.

Conflict of interest

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Reply: Maternal vaccination: moving the science forward[†]

Sir,

We thank Dr Dauby for his interest in our review (Faucette *et al.*, 2015), and share his appreciation of the progress and confidence in the promise of maternal vaccination as a strategy to combat maternal and neonatal infections. Despite the success of selected maternal vaccines, we contend that pregnancy-associated immune modulations could cause suboptimal or qualitatively different vaccine responses. Supporting this notion are the numerous studies showing that both human (Christiansen *et al.*, 1976; Moore *et al.*, 1983; Valdimarsson *et al.*, 1983; Iwatani *et al.*, 1988; Watanabe *et al.*, 1997; Mahmoud *et al.*, 2001; Kraus *et al.*, 2012; Sperling *et al.*, 2012) and mouse pregnancies (Medina *et al.*, 1993;

Medina and Kincade, 1994) are associated with substantial modulations in the B cell compartment. Dr Dauby claimed that such changes in B cells during human pregnancy seemed rather limited and did not appear to affect B cell function, as suggested by recent studies showing similar proportions of first and second trimester B cell subsets (Dauby *et al.*, 2014), rate of seroconversion (Sperling *et al.*, 2012) and immunogenicity (Munoz *et al.*, 2014) in response to vaccination in pregnant and non-pregnant women. It is, however, important to note that the proportion values do not provide direct information on the absolute numbers of B cell subsets. Furthermore, seroconversion rate or immunogenicity does not reflect the diversity or quality of the humoral immune repertoire, such as the degree of somatic hypermutation or neutralizing function. Therefore, the impact of pregnancy-associated changes in the B cell compartment on humoral immune function remains to be carefully elucidated.

Dr Dauby further suggested that B cell-associated quantitative changes occur only in the third trimester, based on findings from his lab and others (Kraus *et al.*, 2012; Dauby *et al.*, 2014). The reduced numbers of circulating B cells have been well documented in the third trimester, but a number of studies found that the reduction in circulating B cell numbers occurred earlier in pregnancy (Moore *et al.*, 1983; Valdimarsson *et al.*, 1983; Iwatani *et al.*, 1988; Watanabe *et al.*, 1997). Considering that the optimal timing of Tetanus, diphtheria and pertussis vaccination (Tdap) recommended by the Centers for Disease Control and Prevention is between 27 and 36 weeks of gestation (Centers for Disease Control and Prevention, 2013) and that the highest trivalent IIV vaccine response rate was seen in the third trimester (Sperling *et al.*, 2012), the substantial reduction in circulating B cell numbers consistently found in the third trimester is likely to impact vaccine response during this critical window. While many studies on the role of reproductive hormones, such as estrogen, that are implicated in modulating B cell function during pregnancy was conducted in mice, the effect of estrogen on human B cell maturation, albeit indirectly, parallels the findings in mouse B cells (Paavonen *et al.*, 1981). In conclusion, due to the complexity of humoral immune modulation, a paucity of data on the B cell compartment in systemic and mucosal secondary lymphoid organs, which are the inductive sites of vaccine immunity distinct from the circulation, and a lack of molecular and functional assessment of the vaccine-induced antibody repertoire during pregnancy, it is presumptuous to conclude that 'B cell compartments, including naïve and memory B cells, appear poorly affected by pregnancy and response to both neo and recall antigens is intact during pregnancy'. Coupled with the heightened ethical and medical concerns of vaccine safety in pregnancy, it is important to exercise caution and combine clinical readouts with basic immunological insights in the development, evaluation and improvement of maternal vaccines, particularly for less well-studied vaccines and in women susceptible to high-risk pregnancies, such that this promising public health strategy can be made safer and more efficient to broader populations against a wider range of infections.

Conflict of interest

The authors declare no competing financial interests.

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[†]The second author of our review, Benjamin L. Unger, has left our institution and could not be contacted.

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