

et al., 1994; Englund et al., 1995; Troisi et al., 1997; Dagan et al., 2000; Kanra et al., 2000; Crowe et al., 2001; Getahun and Heyman, 2009), although cell-mediated immune responses are not affected (Martinez et al., 1997, 1999; Siegrist et al., 1998a, b). The inhibitory effect on infant response to vaccination has been, however, highly variable among different vaccines and even different studies of the same vaccine (Siegrist, 2003).

Many mechanisms of how maternal antibodies may inhibit infant humoral immune response to vaccines (Table II) can be postulated, some of which are based on the understanding of the immunosuppressive mechanism of passive intravenous immunoglobulins (IVIGs) (Schwab and Nimmerjahn, 2013). However, studies on how maternal antibodies may actually interfere with vaccine-induced humoral immunity in infants are needed, as maternal antibodies differ from IVIGs in quantity, structure, composition and function, such as half-life, glycosylation pattern, isotype and affinity for antigens and Fc receptors, and may interfere with the infant immune response via distinct mechanisms from those used by IVIGs. For example, the significant increase in the production of maternal asymmetric IgG with an extra carbohydrate moiety in one of the F(ab') domains during pregnancy (Gutierrez et al., 2005) may allow such IgG molecules to uniquely function as univalent blocking antibodies against vaccine antigens differently from IVIGs in infants (Pasetti et al., 1997). Since maternal antibodies decline in the infant, interference of the infant humoral immunity to vaccination was found to mainly impact primary immunization in early infancy but not subsequent boosting (Glezen, 2003). However, this should not be a reason to dismiss maternal immunization, as a reduced antibody titer after infant vaccination may be acceptable if the high morbidity and mortality can be mitigated in the first months of life by maternal vaccination. Indeed, studies in mice show that maternal antibodies can promote immune maturation in the offspring (Malanchere et al., 1997; Fink et al., 2008). The pros and cons of maternal vaccination on the immune responses to any given infant vaccination protocol should therefore be evaluated individually.

Humoral immune modulations in pregnancy that influence vaccine efficacy and safety

All of the current maternal vaccination formulations are initially designed for and tested in the non-pregnant population. However, substantial immune modulations take place both systemically and in the reproductive mucosa during different stages of pregnancy, highlighting the distinct possibility of sub-optimal or qualitatively different vaccine responses in pregnant women. Research is thus needed to elucidate pregnancy-associated immune alterations in both normal and complicated pregnancies that can influence vaccine responses. The various pregnancy-associated changes in the T, natural killer, myeloid, cytokine and chemokine compartments have been discussed in several excellent reviews (Moffett and Loke, 2006; Mor and Cardenas, 2010; Chen et al., 2012; Pazos et al., 2012a; Erlebacher, 2013). As B cells are the final effectors of humoral immunity, we focus on the modulations in the B cell compartment and their potential influence on vaccine-induced antibody response.

The central and peripheral B cell compartments undergo quantitative changes during pregnancy, with a contraction of peripheral B cell numbers (Fig. 2). Initial studies in mice showed a profound reduction of B cell precursors in the bone marrow from early pregnancy, which was likely mediated by estrogen (Medina et al., 1993, 2000). Consistently, the overall antibody titers to influenza infection are lower in pregnant mice (Medina and Kincade, 1994; Smithson et al., 1998; Chan et al., 2010). Similar changes have also been found in humans by many studies (Christiansen et al., 1976; Moore et al., 1983; Valdimarsson et al., 1983; Iwatani et al., 1988; Watanabe et al., 1997; Mahmoud et al., 2001a). Of note, steroid hormones regulate humoral immunity at multiple stages of B cell development. For example, the very early precursors of pro-B cells are particularly sensitive to negative regulation by

Table II Postulated mechanisms of maternal antibody-mediated inhibition of infant humoral immune response to vaccination.

Mechanism		Supporting references
F(ab') ₂ -dependent	Clearance of vaccine antigens by maternal IgG via opsonization and subsequent FcγR-mediated phagocytosis	Getahun and Heyman (2009)
	Neutralization of live viral vaccine epitopes by maternal IgG Inhibition of infant B cell recognition of vaccine epitopes by maternal IgG via antigenic masking	Albrecht et al. (1977) and Naniche (2009) Wiersma et al. (1989), Jelonek et al. (1996), Nohynek et al. (1999) and Getahun and Heyman (2009)
Fc-dependent	Clearance of vaccine antigens by maternal IgG via FcγR-mediated phagocytosis after antigen opsonization	Getahun and Heyman (2009)
	Inhibition of infant B cell activation, survival and antibody production by maternal IgG via the inhibitory receptor FcγRIIB	Victor et al. (2010) and Kim et al. (2011)
	Inhibition of infant antigen-presenting cells by maternal IgG via the inhibitory receptor Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-integrin (DC-SIGN), also called CD209	Anthony et al. (2008)
	Saturation of infant endothelial or myeloid FcRn by maternal IgG and acceleration of catabolism of vaccine-induced infant IgG	Vieira and Rajewsky (1988), Junghans and Anderson (1996), Hansen and Balthasar (2002) and Li et al. (2005)
	Inhibition of infant dendritic cells (DCs) by ingested and absorbed maternal IgA via FcαRI	Pasquier et al. (2005) and Kanamaru et al. (2008)
	Inhibition of infant B cells and follicular DCs and macrophages by ingested and absorbed maternal IgA via Fcα/μR	Honda et al. (2009)