Exploring maternal-infant linked influenza antibody kinetics using a unified population model

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Objective: Inactivated influenza vaccine is recommended during pregnancy to provide passive immunity against influenza to the infant. However, the kinetics of transplacentally acquired immunity have not been assessed in a comprehensive quantitative manner. Our objectives were to 1) develop a physiological model that describes the effects of vaccination in increasing maternal influenza antibody levels; 2) model infant influenza antibody kinetics and evaluate the influence of maternal vaccination; 3) develop a unified maternal-infant physiological model that simultaneously describes influenza antibody transfer and the effects of maternal immunization.

Methods: Pregnant women 18 – 45 years of age were enrolled from 01/2012 through 05/2014 (three influenza seasons) from University of Utah Health obstetric clinics. Antibody data from the A/California strain (01/2012 – 05/2014) was analyzed. Infant serum samples were collected at delivery, and 2 and 6 months of age. Influenza antibody levels were determined by hemagglutination inhibition (HAI) assay. Population models were developed using NONMEM 7.3 (ICON Development Solutions, Ellicott City, MD, USA). Demographic characteristics including birth weight, gestational age, sex and ethnicity, together with maternal vaccination status (yes=1, no=0), were evaluated as potential covariates. Covariate screening was conducted in a stepwise (forward inclusion, p<0.05; backward elimination, p<0.01) manner using PsN modules.

Results: A total of 70 pairs of mother/infant subjects were included in analysis. Infant subjects had a median (5th - 95th quantiles) gestational age of 39.3 (38 – 41) weeks, birth weight of 3240 (2760 – 3903) grams. 60% (42/70) of infants were male and 31% (22/70) were Hispanic/Latino.

Maternal antibody kinetics and vaccination influence were best described by a one-compartment model with constant rate generation ($R_{in}$) and first-order elimination ($R_{out0}$). The initial antibody amount was parameterized with a log normally distributed parameter $A_0$. The vaccine effect was parameterized by an amplification factor ($VAC$) that immediately increases $A_0$ upon vaccination. The parameter estimates were as follows: $A_0$, 9.2 (95% CI: 6.7 – 11.6) titer; $R_{out0}$, 0.005 (95% CI: 0.001 – 0.01) day$^{-1}$; $VAC$, 2.7 (95% CI: 1.9 – 3.6).

Infant immunity kinetics were best described by a one-compartment model with first order elimination. The model was parameterized with the initial antibody level at delivery ($A_1$) and the elimination rate ($R_{out1}$). The parameter estimates were as follows: $A_1$, 48.9 (95% CI: 24.6 – 73.2) titer; $R_{out1}$, 0.018 (95% CI: 0.016 – 0.021) day$^{-1}$. Vaccination status was detected as a significant covariate on $A_0$ (p<0.005), while the incorporation of other covariates did not improve model fitting significantly.

Conclusions: Maternal influenza antibody kinetics were described by a one-compartment model with constant rate generation and first-order elimination. Infant influenza antibody kinetics were described by a one-compartment model with first-order elimination. Maternal vaccination significantly increased infant influenza antibody levels at delivery. Future analyses will link the infant and maternal models and evaluate the impact of breast feeding on infant influenza immunity.

**Figure 1.** Model structure of maternal/infant influenza antibody level association. $A_0$: maternal antibody level; $A_1$: infant antibody level; $R_{in}$: rate of maternal antibody generation; $R_{out0}$: rate of maternal antibody decay; $R_{out1}$: rate of infant antibody decay; $R$: transplacentally antibody exchange ratio; BMF: breast milk feeding influence.