2729. mRNA Vaccines Encoding Conserved Influenza Antigens Induce Robust and Durable Immunity in Rhesus Macaques

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Background: In response to immune pressure, influenza virus evolves, producing drifted variants capable of escaping immune recognition. One strategy for inducing a broad-spectrum immune response that can recognize multiple antigenically diverse strains is to target conserved proteins or protein domains. To that end, we assessed the immunogenicity of mRNA vaccines encoding the stem domain of hemagglutinin (HA) or nucleoprotein (NP) in nonhuman primates (NHPs).

Methods: Rhesus macaques were immunized three times intramuscularly, at 28 day intervals, with lipid nanoparticle-encapsulated mRNA encoding either HA stem (Yassine et al, 2015) or NP. Serum and PBMCs were collected up to 14 or 24 weeks, respectively, after the last vaccination. The magnitude and durability of humoral and cell-mediated immunity were evaluated. ELISA, competition ELISA, an *in vitro* antibody-dependent cell-mediated cytotoxicity (ADCC) reporter bioassay, and microneutralization assays were used to characterize serum immune responses. Intracellular cytokine staining (IFN-gamma and IL-2) was used to assess antigen-specific T-cell responses.

Results: HA stem-immunized NHPs developed a robust anti-stem binding titer after a single vaccine dose, and after two doses, serum antibodies recognized several antigenically distinct Group 1 HA proteins. This broad antibody response persisted for at least 14 weeks post-dose 3 (PD3). Serum antibodies showed ADCC activity and competed with a well-characterized broadly neutralizing antibody, CR9114, for binding to HA stem; however, the polyclonal serum had only minimal activity against a panel of H1N1 viruses in a microneutralization assay. HA-specific CD4+ T-cell responses were detectable PD3. A robust antibody binding response was also detected in NP-vaccinated NHPs, and titers remained high for at least 14 weeks PD3. Additionally, these animals developed robust NP-specific T-cell responses that persisted for at least 24 weeks PD3. On average, 0.5% of CD4+ and 4% of CD8+ T cells produced IFN-gamma in response to NP peptide stimulation at the peak of the response, 2 weeks after the last vaccine dose was administered.

Conclusion: Lipid nanoparticle-encapsulated mRNA vaccines encoding conserved influenza antigens induce a robust and durable immune response in NHPs.

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2730. Estimating Deaths Attributable to Influenza Mortality Using Traditional and Novel Forecasting Methods

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Background: Seasonally-adjusted linear models ('Serfling' models) serve as an important surveillance measure to estimate influenza (flu) attributable deaths for resource allocation to public health programs (e.g., vaccination campaigns). We compared performance of traditional time-series and viral activity-based models to a novel open-source R-package 'Prophet' for estimating the number of deaths attributable to influenza per season.

Methods: We evaluated deaths from the 122-Cities Mortality Reporting System which reports the total number of death certificates where pneumonia or flu was listed as a contributing cause of death. Models were fitted to 2010–2015 influenza seasons. The first Serfling model (M1) used baseline periods of low-endemicity (summer months) to estimate attributable deaths during a flu season (OCT–MAY), the second Serfling model (M2) incorporated both baseline and virology data (count laboratory proven flu cases in a given period). The Prophet model (M3) uses generalized additive models incorporating annual, seasonal terms and viral activity data. The difference between observed deaths, and those predicted by each model in the absence of flu were 'attributable death." Epidemic weeks exceeded the 95% upper prediction interval. Model performance was assessed by Root Mean Square Error (RMSE).

Results: From 2010 to 2015, the average deaths due to pneumonia and influenza per season numbered 824 per week (total 198,692). Compared with the traditional Serfling model (M1), the Prophet model estimated 52% more influenza-attributable deaths (13,443 vs. 8,800) and more epidemic weeks (25 vs. 10) with lower RMSE (75.9 vs. 95.3 [lower is better]). Compared with the viral activity-based model (M2), the Prophet model estimated 6% fewer attributable deaths (13,443 vs. 14,326), with more epidemic weeks (25 vs. 19) and lower RMSE (RMSE 75.9 vs. 92.6).

Conclusion: Generalized additive models, implemented through the R-package Prophet, are superior in terms of reducing model prediction error for influenza mortality vs. traditional models. Based on superior model performance, the attributable mortality estimated by these novel models may be preferred over traditional regression models. This study was funded by Sanofi Pasteur.

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2731. Does Last Season's Influenza Vaccination Affect Current Season's Vaccine Effectiveness in Young Children?

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Background: We evaluated influenza VE over two consecutive years vs. the current season against influenza illness during two H3N2-predominant seasons in children receiving care at emergency/urgent care (ED/UC) facilities in metropolitan Colorado.

Methods: We conducted a test-negative case–control analysis of 1478 children aged 6 months to 8 years enrolled at Children's Hospital Colorado ED/UC with influenza like illness during the 2016–2017 and 2017–2018 influenza seasons. The primary outcome was PCR-confirmed influenza and vaccination status was confirmed using electronic medical record and parental interviews. Vaccination status was defined as completely vaccinated (all doses of influenza vaccine according to child's age); partially or not vaccinated children were defined as unvaccinated. Multivariable logistic regression models adjusted for high-risk medical condition, age, race and insurance status were used to calculate odds ratios (OR) and 95% confidence intervals. Vaccine effectiveness was calculated as $(1 - OR) \times 100$.

Results: Of the 1224 (82.8%) children enrolled in the study with known vaccination status for both seasons, 361 (29%) tested positive for influenza. Overall, VE against influenza was 49% (95% CI, 33–61%) after adjusting for other covariates in the model. VE did not differ significantly between those vaccinated in both seasons and those vaccinated in only the current season (VE 69%, 95% CI 41–115) (Table 1).

Conclusion: Our estimates of influenza VE for two predominantly H3N2-influenza seasons in Colorado are comparable to the CDC -VE for children 6 months to 8 years. VE against ED or UC-attended influenza illness in children did not vary significantly by prior seasons' vaccination status.

Table 1—Vaccine Effectiveness over 2016-17 and 2017-18 influenza seasons, n= 1224

Predictor (vaccination status)	Crude OR (95%CI)	Adjusted[a] OR (95%CI)	Adjusted Vaccine effectiveness (%)	Adjusted p-value
Current season vs neither	0.45 (0.12,0.65)	0.29 (-0.16,0.56)	71 (44,116)	0.17
Both seasons vs neither	0.36 (0.14,0.52)	0.51 (0.32,0.65)	49 (35, 68)	<.0001
Both seasons vs current season only	-0.16 (-0.88,0.28)	0.31 (-0.15,0.59)	69 (41,115)	0.15
Both seasons vs prior season only	0.63 (0.47,0.74)	0.56 (0.36,0.70)	44 (30,64)	<.0001

a-adjusted for high risk medical condition, age, race and insurance status

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2732. Estimate of the Effectiveness of Influenza Vaccine among Children for the 2017–2018 Season

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Background: The 2017–2018 influenza season was one of the deadliest in decades, with 180 pediatric deaths, 80% among children who did not receive the vaccine. Circulating influenza strains change periodically, making it important to determine vaccine efficacy on an annual basis specifically in susceptible populations. The primary aim of our study was to estimate the effectiveness of the influenza vaccine for the 2017–2018 season. Secondary aims were to determine effect of weaning immunity and of previous season vaccination.

Methods: Children 6 months to 17 years tested for influenza during the 2017–2018 season at Children's Hospital of New Orleans were included. Clinical charts were reviewed, and immunization status confirmed via the Louisiana Immunization Registry. Using a multivariable logistic regression model vaccine effectiveness (VE) was estimated by comparing vaccination status of influenza-positive vs. influenza-negative cases with the formula VE = $(1 - OR) \times 100\%$.

Results: 4,825 children were included; 22% of them tested positive for influenza, mostly influenza A (61.9%); 21% had received an influenza vaccine prior to illness: 14% among the influenza-positive and 23% among influenza-negative ($P < 0.0001$). Overall, VE for the 2017–2018 influenza season was 43% (95% CI 30, 53); 44% for influenza A and 38% for influenza B. While receiving current year (2017–2018) vaccine had the most effect, receiving the previous year (2016–2017) vaccine had additional benefit. We found no waning immunity of the vaccine for the 2017–2018 season.

Conclusion: Influenza VE was modest for children in the local area of New Orleans and similar to the CDC's findings for the nation as a whole. Previous year vaccination had a small, but significant benefit and there was no evidence of waning immunity in our cohort. Ongoing national and local surveillance is important to understand the benefit of influenza vaccination.

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