

# Immunogenicity of meningococcal conjugate vaccine in HIV-infected youth

G Siberry<sup>1</sup>, J Lujan-Zilbermann<sup>2</sup>, P Williams<sup>3</sup>, M Warshaw<sup>3</sup>, M Decker<sup>4</sup>, B Heckman<sup>5</sup>, E Demske<sup>6</sup>, J Read<sup>1</sup>, P Jean-Philippe<sup>7</sup>, S Nachman<sup>8</sup>, & IMPAACT P1065 Team

NICHD-PAMA Branch, NIH, Bethesda, MD<sup>1</sup>, USF Coll. Med., Tampa, FL<sup>2</sup>, Harvard Sch. Pub. Health, Boston, MA<sup>3</sup>, Sanofi Pasteur Inc., Swiftwater, PA<sup>4</sup>, FSTRF, Amherst, NY<sup>5</sup>, SSS, Silver Spring, MD<sup>6</sup>, HJF-DAIDS, Bethesda, MD<sup>7</sup>, SUNY Stony Brook<sup>8</sup>

## Original Abstract # S-104

**Background:** Quadrivalent Meningococcal Vaccine (MCV4) is routinely recommended for adolescents in the United States. Healthy youth respond to MCV4 at high rates (80-97%), varying by meningococcal serogroup (SG). There are no data regarding the immunogenicity of MCV4 in HIV-infected youth.

**Methods:** P1065 is a Phase I/II safety and immunogenicity trial of MCV4 in HIV-infected youth (11-24 years old) performed at 27 clinical sites of the IMPAACT network in the US. All subjects received 1 dose of MCV4 at entry; at 24 weeks, subjects in Group 1 (CD4  $\geq$ 15%) were randomized to receive a 2nd dose vs. no dose of MCV4, while all eligible subjects in Group 2 (CD4 <15%) received a 2nd dose. Immunogenicity after the 1st MCV4 dose was evaluated as the proportion of subjects with a 24-fold rise in serum bactericidal antibody (SBA) against each meningococcal SG (SG A, C, Y and W-135) at 28 days after immunization. Multivariable logistic regression analysis (MV) was used to assess the association of age, CD4 percentage, gender, CDC illness class, and viral load (VL) on immunogenic response to SG C.

**Results:** Of 318 eligible enrolled subjects who received at least 1 dose of MCV4, 297 had serology results. Enrollment was stratified by CD4%: CD4 <15% (n=34, 11%), CD4 = 15-24% (n=119, 40%) and CD4  $\geq$ 25% (n=144, 48%). The median age was 18 years; 59% were male, 51% were black, and 49% had VL  $\leq$ 400 copies/ml at entry. The proportion with 24-fold SBA titer rise to SG A, C, Y, and W-135 were 69% [ $\pm$ 3%], 53% [ $\pm$ 3%], 63% [ $\pm$ 3%] and 73% [ $\pm$ 3%], respectively. Eighty-eight percent of subjects had 24-fold SBA titer rise to at least one SG. When excluding the subjects with baseline immunity (SBA titer  $\geq$ 1:128) to each SG [A, 41%; C, 12%; Y, 35%; W-135, 15%], the proportions with 24-fold SBA titer rise to SG A, C, Y, and W-135 were 77% [ $\pm$ 3%], 51% [ $\pm$ 3%], 66% [ $\pm$ 3%] and 73% [ $\pm$ 3%], respectively. In MV, lower entry CD4% stratum, VL >10,000 copies/ml, CDC Class C, and female gender were associated with significantly lower odds of response to SG C.

**Conclusion:** Many HIV-infected youth naturally acquire meningococcal immunity, especially to SG A and Y. MCV4 is immunogenic in most HIV-infected youth, but response rates are lower than in healthy youth. Higher CD4 ( $\geq$ 15%) and lower HIV VL were associated with greater immunogenicity.

**Note:** abstract based on data as of 9/9/2008; remainder of poster results updated to reflect data as of 1/5/2009.

## Introduction

MCV-4 is a meningococcal conjugate vaccine containing *N. meningitidis* serogroups A, C, Y, and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxin protein. It was approved by the FDA in 2005 for  $\geq$  11 year olds. HIV infection is a likely but unproven risk factor for meningococcal infection. Most perinatally-acquired and all new adolescent cases of HIV infection in the U.S. are age-eligible for MCV4. Healthy youth respond to MCV4 at high rates (80-97%), varying by meningococcal serogroup (SG), but immunogenic response to vaccines, including conjugate vaccines, can be impaired in HIV-infected patients. However, there are no data regarding the immunogenicity of MCV4 in HIV-infected youth.

## Objective

The objective of this analysis was to evaluate the baseline immunogenicity of a single dose of MCV4 in HIV-infected youth.

## Methods- Study Design

- P1065 is a phase I/II study of safety and immunogenicity of MCV4 in HIV+ youth aged 11-25 yrs
- **Eligibility Criteria:**
  - On stable antiretroviral therapy (ART) or on no ART for at least 90 days prior to vaccine
  - No personal or family history of Guillain-Barré Syndrome; no receipt of meningococcal conjugate vaccine at any time, or meningococcal polysaccharide vaccine within last two years
- **Study Design:**
  - Subjects were stratified by CD4% into three groups: <15%, 15%-24%, and  $\geq$ 25%
  - All subjects were administered the MCV4 vaccine at study entry.
  - Serum drawn for meningococcal assays at entry (pre-vaccine) and 4 week visits
  - (Additional vaccine dose and longer term immunogenic responses in progress).
- **Immunogenicity:**
  - Rabbit serum bactericidal assay (rSBA) against each SG, performed by Sanofi-Pasteur laboratories, employing assay used for MCV4 licensure
  - Positive Response: 4-fold rise in rSBA titer from pre-vaccine level
  - Absolute serologic titer correlates of immunity:  $\geq$ 1:128 Immune; <1:8 Susceptible
  - Multivariable logistic regression analysis (MV) was used to assess the association of age, CD4 percentage, gender, CDC illness class, race, ethnicity, perinatal HIV infection status, and viral load on immunogenic response to SG C.

## Results

- 324 participants enrolled, 318 eligible subjects received first MCV4 dose, and 306 of these 318 (96%) have available serology results.
- Of these 306 participants, 180 (59%) were male, 154 (50%) were Black, 115 (38%) reported Hispanic/Latino ethnicity, and median age was 17 (range 11-24 years). Baseline clinical characteristics are shown in Table 1. There were no significant differences between the 306 subjects with and the 12 subjects without serology results in either demographic or clinical characteristics.
- The percent with baseline immunity to each SG [ $\pm$ SE] was A: 41% [ $\pm$ 3]; C: 11% [ $\pm$ 2], W135: 15% [ $\pm$ 2], and Y: 35% [ $\pm$ 2] (see Figure 1).
- A positive response (4-fold rise in titer) to MCV4 [ $\pm$ SE] was observed for 68% [ $\pm$ 3] for SG-A, 52% [ $\pm$ 3] for SG-C, 73% [ $\pm$ 3] for SG-W135, and 63% [ $\pm$ 3] for SG-Y (see Figure 2).
- Restricting the analysis to those without baseline immunity (titer <1:128) yielded comparable response rates, with the exception of an increase in response rate for SG-A from 68% to 76%; all other response rates remained within 1-2% of those shown in Figure 2.
- Based on a multivariable logistic regression model, lower entry CD4%, higher viral load, being on HAART, and female gender were associated with significantly lower odds of response to SG C.

## Results – Tables and Figures

Table 1: Characteristics of 306 P1065 Participants with Serology Data

Clinical Characteristic		N (%)
CD4% at Screening/Entry	Group 2: CD4% <15	36 (12%)
	Group 1: CD4% 15- $\geq$ 25%	122 (40%)
	Group 1: CD4% $\geq$ 25%	148 (48%)
VL at entry (copies/mL)	$\leq$ 400	148 (48%)
	401-10,000	70 (23%)
	>10,000	88 (29%)
	Median	613
CDC Class C at Entry		75 (25%)
Perinatally HIV-Infected		204 (67%)
ART Regimen at MCV4 Dose	HAART with PI	166 (54%)
	HAART with NNRTI (no PI)	51 (17%)
	Other ART	16 ( 5%)
	No ART	73 (24%)

Figure 1: Positive Immunogenicity (rSBA Titer  $\geq$ 1:128) at Week 0 (pre-vaccination) and Week 4 (post-vaccination)

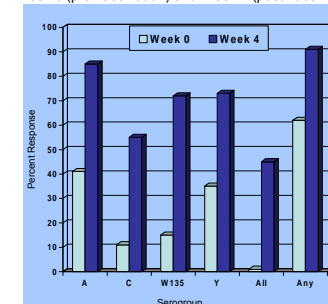


Figure 2: 4-fold Immunogenicity Response in P1065 and in Healthy HIV-uninfected Youth [Keyserling et al 2005]

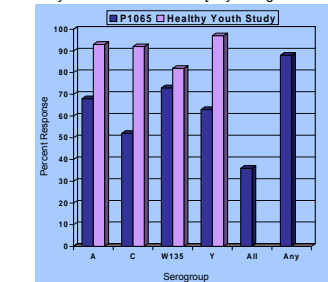


Table 2: Response Rates and Multiple Logistic Regression Results for Immunogenicity Response to SG-C as predicted by Clinical Characteristics

Characteristic	N	Response Rate to SG-C (unadjusted)	Adjusted Odds Ratio for Response	95% Confidence Interval	P-value	
CD4%:	<15%	34	12%	0.11	(0.03,0.34)	<0.001
	15-24%	120	48%	0.56	(0.32,0.96)	
	>25%	145	66%	1.00	(ref)	
VL (copies/mL)	$\leq$ 400	145	64%	1.00	(ref)	0.001
	401-10,000	69	54%	0.50	(0.26,0.98)	
	>10,000	85	31%	0.23	(0.11,0.50)	
On HAART: Yes	210	50%	0.33	(0.17,0.65)	0.001	
	No	89	56%	1.00	(ref)	
Sex:	Male	175	57%	1.62	(0.97,2.73)	0.07
	Female	124	46%	1.00	(ref)	

## Conclusions

- Many HIV-infected youth naturally acquire meningococcal immunity, especially to serogroups A and Y.
- MCV4 is immunogenic in most HIV-infected youth, but response rates appear lower than those reported for healthy youth. Higher CD4 ( $\geq$ 15%) and lower HIV VL were associated with greater immunogenicity.
- A booster dose of MCV4 may be required for HIV-infected youth to result in desired levels of immunogenicity.