

13 Assessing Safety of Simultaneous/Combination Vaccinations (SCV)

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Objective: Given the large number of permutations of SCV possible, especially with new vaccine-preventable diseases, pre-licensure evaluation of the safety of each permutation of SCV is limited. We explored the use of VSD for more complete safety data on SCV.

Methods: The VSD links automated immunization and medical records of ~2% of the U.S. population from four Managed Care Organizations (MCO). Using 1992-1995 data from one MCO, we compared the relative incidence of medical visit within one week after various SCV to that after receipt of OPV alone.

Results: The safety of nine permutations of MSV among 17,783 children 0-11 months of age and 17 permutations of MSV among 13,396 children 12-23 months of age was evaluated. For all permutations, the relative incidence of medical visits post-MSV did not differ significantly from that post-OPV. The sample size, relative risk and 95% confidence interval for the most common permutations in 0-11 month olds were: DTP+HIB (8,903, 0.86, 0.42-1.85), DTP+HIB+OPV (20,106, 0.72, 0.51-1.01), DTP+HIB+Hep.B+OPV (9,270, 0.54, 0.38-0.76). For 12-23 month olds: DTP+OPV (5,495, 0.8, 0.58-1.11) and DTP+HIB+MMR+OPV (3,790, 0.73, 0.52-1.02). These results were similar when adjusted for frequency of medical visits within a week before vaccination, a possible cause of confounding by contraindication.

Discussion: Our data suggest that: 1) VSD is a useful means to expand data on safety of SCV post-licensure, 2) SCV is a safe way to complete the increasingly complex childhood immunization schedule, and 3) expansion of similar analyses to the entire VSD data set is warranted.

15 Safety of a Combined Diphtheria-Tetanus-Acellular Pertussis (DT-ricomponent Pa)-Hepatitis B (HB)-Inactivated Poliovirus (IPV) Admixed with Haemophilus influenzae type b (Hib) Vaccine in Infants

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The comparison of injection site reactions in combination vaccine studies is problematic. When local reactions at a single injection site for the combination vaccine are compared to local reactions at more than one site for simultaneously administered separate component vaccines, a seemingly incongruous comparison must be made. One method commonly used is to compare the single combination vaccine injection site to the most reactogenic of the multiple injection sites, but this does not account for reactions that invariably occur at other separate injection sites. We recently completed an open, randomized, multicenter trial which evaluated the safety of a combined DTPa-HB-IPV admixed with a lyophilized Hib (mfr by SB Biologicals) given as a single injection compared to separate, concurrent administration of DTPa (Infanrix[®]) given in one limb; HB (Engerix-B[®]) and Hib (OmniHib[®]) both given in the opposite limb, along with oral poliovirus (OPV) (ORIMUNE[®]) to 268 healthy infants at 2, 4, and 6 months of age. Rates of local reactions at the DTPa-HB-IPV/Hib injection site were comparable to those reported at the most reactogenic (DTPa alone) separate injection site (pain: 23.5% vs. 23.9%; redness: 28.9% vs. 26.0%; swelling: 17.9% vs. 16.6%, respectively); rates of systemic symptoms were also similar. In order to account for the fact that children who received the combination vaccine only had injection reactions at one site (one limb) whereas those in the control group could experience local reactions at three sites (two limbs), a further analysis was undertaken.

% of Doses in Which One or Both Limbs Were Involved

		DTPa-HB-IPV/Hib*				DTPa.HB.Hib**				Total
		D1	D2	D3	All	D1	D2	D3	All	
Pain	1 limb*	31	23	16	24	13	7	13	11	30
	2 limbs**	—	—	—	—	26	16	13	19	
Redness	1 limb	26	30	30	29	12	7	17	12	31
	2 limbs	—	—	—	—	17	9	23	19	
Swelling	1 limb	17	19	18	18	11	7	14	11	22
	2 limbs	—	—	—	—	9	3	11	11	

D=Dose; All=All Doses; *1 injection; **3 injections

Remark: The percentage of doses followed by a report of a specific local reaction in at least one limb was slightly higher overall in the separate injection (DTPa, HB, and Hib) group than in the single injection (DTPa-HB-IPV/Hib) group. Additionally, 1/2 to 2/3 of all reports in the triple injection group involved both limbs.

14 A Pilot, Ascending Dose-Study of the Safety and Adjuvant Activity of Subcutaneous (SC) Recombinant Human IL-12 (rhIL-12) with Hepatitis B Vaccine in Healthy, Older Adults

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Objective: Assess the safety and adjuvant effect of rhIL-12 in healthy adults ages 50-70 years.

Study Design: Doses of 1, 2, or 4 mcg of rhIL-12 were evaluated. Subjects were enrolled in sequential cohorts to receive the standard 3 dose regimen of intramuscular (IM) Recombivax[®] 10 mg at days 0, 30, and 180. All subjects received SC injections of rhIL-12 or placebo concurrent with the vaccine administration within 5 cm of the IM injection site. Within a dosing cohort, subjects were randomly assigned to receive 0, 1, or 2 injections of rhIL-12 or placebo. Escalations to a higher-dose cohort occurred after a demonstration of a satisfactory safety experience within the prior dosing cohort.

Results: Preliminary safety and serologic data are available. A total of 96 subjects were enrolled (24 to placebo; 24 each to 1, 2, and 4 mcg of rhIL-12). The overall pattern and severity of observed adverse events were similar between vaccine/placebo and vaccine/rhIL-12 recipients. The 4 mcg dose of rhIL-12 had more adverse events than the lower dose levels or placebo. Local injection site reactions, headache, asthenia, myalgia, nausea and upper respiratory symptoms were most commonly reported, and were of mild or moderate severity. Two injections of rhIL-12 were associated with an increased geometric mean titer (MIU/ml) of anti-HBsAb 30 days after the final vaccine injection compared with vaccine only (placebo only: 208; 1 mcg: 1813 (p<0.01); 2 mcg: 890 (p>0.05); 4 mcg: 1728 (p<0.01)).

Summary: Subcutaneous administration of low doses of rhIL-12 was well-tolerated, with evidence of adjuvant effect, when administered concurrently with intramuscular hepatitis B vaccine.

16 Response to Japanese Encephalitis Vaccine in HIV-infected Children, Bangkok, Thailand

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JE vaccine is a component of the EPI in northern Thailand, where JE and HIV infection both are prevalent. To evaluate JE vaccine immune response and safety in HIV-infected children, we retrospectively studied HIV-infected and uninfected children, born to HIV-seropositive mothers, who had received 2 JE vaccine doses at 12 months as part of routine pediatric care. Excluding 5 children with pre-immunization antibodies, 5 of 14 (36%) HIV-infected and 18 of 27 (67%) HIV-uninfected children developed JE neutralizing antibody titers > 10 (OR 0.3, P = 0.06); the absolute difference in response was 31% (95% C.I. 0-61.7%). Among those with positive titers, the GMT of HIV-infected children was lower than that of control children (15.1 vs. 23.8; P = 0.17). Among HIV-infected children, JE vaccine-responders had slightly higher CD4+ counts than non-responders (1750 vs. 1400; P = 0.6). No significant vaccine-associated adverse events were noted.