

S13 Bivalent Envelope Vaccines (AIDSVAX™) Evaluated for Efficacy Against Blood-Borne and Sexually Transmitted HIV-1 in Thailand and North America. D.P. Francis,¹ P.W. Berman.¹ ¹VaxGen, Inc., Brisbane, California. Following both historical precedents of other viruses and scientific data specific for HIV-1, a recombinant envelope vaccine (AIDSVAX™) has been developed. Chimpanzee immunization experiments indicated that AIDSVAX™ could protect against both homologous and heterologous HIV-1 challenge. After human Phase I and Phase II studies indicated that the vaccine was safe and highly immunogenic, bivalent formulations were developed to protect against virus subtypes circulating in North America and Thailand. These bivalent vaccines, like their monovalent predecessors, are highly immunogenic, inducing binding and neutralizing antibodies in essentially all recipients. Moreover, again similar to their monovalent counterparts, adverse events associated with receipt have been limited to local reactions at the injection site. A Phase III study of AIDSVAX™ B/B was started in June 1998 in over 40 cities in North America. A Phase III study of AIDSVAX™ B/E will start in February 1999 in Bangkok, Thailand. Both studies are designed to confidently (p=.05) detect an efficacy of at least 30%. The North American trial (5,000 volunteers) is evaluating protection against sexually-acquired infection, while the Thai trial (2,500 volunteers) will evaluate blood-borne infection. The endpoints for both studies are the same – “sterilizing” immunity, as was observed in the protected chimpanzees, measured by ELISA, and reduced viral load, measured by RNA PCR. Rates of both endpoints will be compared between the vaccine recipients and the placebo recipients.

S14 Testing Tetravalent Live-attenuated Dengue Vaccine Candidates in Human Subjects by Factorial Design. W.Sun, R. Edelman*, K. Eckels, R. Putnak, A. King, N. Kanesa-thasan, and B. Innis. *Univ of Maryland School of Med., Baltimore, MD; Walter Reed Army Institute of Research, Wash. DC. **Introduction:** A tetravalent dengue vaccine (TDV) is needed to protect against all 4 serotypes of dengue. WRAIR has developed 4 live dengue vaccine candidates by serial passage in primary dog kidney cells and combined them to form a tetravalent vaccine. This tetravalent vaccine previously given to 4 healthy adults was fairly well-tolerated and elicited tetravalent neutralizing antibody (Nab) in 2/4 volunteers. The next development milestone was determination of an optimal dose mixture of the 4 vaccine components. **Objectives:** To determine effect of 2 dose levels of each serotype component on reactogenicity and immunogenicity. **Method:** Study design was a 2⁴ factorial: 16 different tetravalent formulations consisting of all possible combinations of either full dose (10⁵-10⁶ pfu/ml) or low (1.5 log dilution) dose of each serotype were made. This design allows detection and estimation of any interaction among the serotypes. Each formulation was given s.c. to 3-5 flavivirus-naïve healthy volunteers by a 2-dose schedule (0 and 1 month). Adverse effects were identified by self-report diaries and clinic visits. The immunogenicity endpoint was development of Nab to all 4 serotypes 28 days after second dose of tetravalent vaccine. **Preliminary Results:** To date 31 volunteers have each received one of 11 tetravalent formulations. Formulations with full dose of DEN-1 were significantly more reactogenic than formulations with low dose (p<.001). Significant difference in Nab seroconversion rates between full dose and low dose occurred only with DEN-1 (100% vs 35%, p<0.01). Nab seroconversion to DEN-4 among tetravalent vaccine recipients occurred less frequently (8%) than among monovalent DEN-4 vaccine recipients (58%; p<0.05). **Conclusion:** 1) Reactogenicity of tetravalent vaccine is associated with dose of DEN-1. 2) Components of the tetravalent vaccine appear to reduce the immunogenicity of DEN-4.

S15 Evaluation of the Safety, Immunogenicity and Virus Shedding of a Live Intranasal Bovine Parainfluenza Virus Type 3 (PIV3) Vaccine in Infants DP Greenberg¹, S Yek², R Yogev², KS Reisinger¹, Ji Ward², MM Blatter⁴, S Holmes⁵, PM Mendelman⁵, KL Coelingh⁵, and I Cho⁵. ¹Child Hosp of Pittsburgh, Pittsburgh, PA; ²UCLA Center for Vaccine Res, Torrance, CA; ³Child Mem Hospital, Chicago, IL; ⁴Primary Physicians Res, Pittsburgh, PA; ⁵Aviron, Mountain View, CA. PIV3 is second to RSV as the most common cause of croup, bronchiolitis and pneumonia in infants. Bovine PIV3 (BPIV3) has significant homology with human PIV3 and it has attenuated replication in the human respiratory tract. **Methods:** To evaluate BPIV3 vaccine, 192 infants were randomized to receive 10⁵TCID₅₀ or 10⁶TCID₅₀ BPIV3 vaccine or placebo by intranasal spray at 2, 4, 6 and 12-15 months of age (other routine vaccines were given concurrently). Safety data were collected after each dose. Sera and nasal washes (to detect viral shedding) were obtained. **Results:** Data through dose 3 are presented. The rates of adverse events were similar between the three groups, and no serious adverse events attributable to the vaccine occurred. After doses 1, 2, and 3, 47%, 34%, and 23% of vaccine recipients, respectively, shed BPIV3. Hemagglutination inhibition (HAI) responses to BPIV3 and proportions shedding BPIV3 are shown below.

Group	N	Pre-dose-1		Post-dose-3		Pre- to post-dose-3 HAI		BPIV3 shedding after any dose	HAI 4-fold rise ^a or BPIV3 shedding
		HAI GMT	HAI GMT	HAI GMT	HAI GMT	4-fold rise ^a	rise ^a		
1) 10 ⁶ TCID ₅₀	62	4.1	6.4 ^b	4.1	6.4 ^b	43% ^b	73% ^b	78% ^b	
2) 10 ⁵ TCID ₅₀	64	4.2	5.4 ^b	4.2	5.4 ^b	42% ^b	57% ^b	80% ^b	
3) Placebo	66	4.0	2.4 ^b	4.0	2.4 ^b	8% ^b	3% ^b	7% ^b	

^a Only 4-fold rises in HAI were adjusted for maternal antibody using 23 day half life; ^b p<0.01, group 1 vs 3 and group 2 vs 3. **Conclusion:** Live attenuated BPIV3 vaccine was 1) well-tolerated when given to infants concurrently with other routine vaccines, 2) induced significant rises of HAI antibody to BPIV3 in most subjects relative to placebo, and 3) resulted in high rates of nasal shedding of BPIV3 (57% - 73%).

S16 Phase I Safety and Immunogenicity Trial of a Recombinant Hepatitis E Virus Vaccine. R. Kuschner¹, J. Sun¹, J. Seriwatana¹, J. Thompson¹, R. Robinson², D. Vaughn¹, D. Fu³, B. L. Innis¹. ¹Walter Reed Army Institute of Research, Washington, DC; ²DynCorp, Rockville, MD; ³SmithKlineBeecham, Bethesda, MD.

Hepatitis E virus (HEV) is a recognized cause of enterically transmitted non A-non B hepatitis in large parts of Asia, Africa, and Mexico. HEV generally causes a self-limited illness, but has been reported to be fatal in up to 25% of pregnant women. HEV is a non-enveloped, positive strand RNA virus tentatively classified in the genera of Hepatitis-E-like viruses in the unknown family. The genome is approximately 7,200 nucleotides in length and encodes three open reading frames (ORF). ORF2 encodes the putative capsid protein. Protection against HEV is believed to be conferred by immune responses, particularly humoral immunity, to the ORF2 antigen. HEV isolates from different geographical regions share the same ORF2 antigenic pattern; it is felt that only one HEV serotype exists. Therefore, the capsid antigen is a likely vaccine candidate. We utilized the baculovirus expression system to produce a purified polypeptide containing truncated ORF2 (amino acid residues 112 to 607) and administered 1 µg, 5 µg, 20 µg, or 40 µg to a total of 88 volunteers on days 0 and 28. A third dose will be given on day 182. Preliminary data suggest the candidate vaccine is well tolerated and immunogenic.