

S17 ChimeriVax™ – novel live, attenuated genetically engineered vaccines against heterologous flaviviruses, based on yellow fever (YF) 17D vaccine. T.P. Monath¹, J. Arroyo¹, T.J. Chambers², S. Delagrave¹, Z. X. Zhang¹, R.A. Weltzin¹, G. Myers¹, K. Soike³, M. Ratterree³, A.D.T. Barrett⁴, B.R. Miller⁵, T. Bhatt⁵, F. Guirakho¹. ¹OraVax Inc., Cambridge Massachusetts; ²St. Louis University, St. Louis, Missouri; ³Tulane Regional Primate Center, Covington, Louisiana; ⁴University of Texas Medical Branch, Galveston, Texas; ⁵Centers for Disease Control and Prevention, Fort Collins, Colorado.

To produce 'ChimeriVax™' vaccine candidates, the prM and E genes of YF 17D vaccine were replaced with the corresponding genes of Japanese encephalitis (JE) or dengue (DEN) viruses. RNA transcribed from full-length chimeric cDNA was transfected into cultured cells, and progeny virus used as vaccine seed. The E protein of the donor virus contains protective antigens, while replicative enzymes are encoded by YF genes. To produce vaccines against neurotropic agents (JE), the donor genes were derived from an attenuated virus (SA14-14-2). Multiple mutations in the SA14-14-2 E gene responsible for attenuation were identified by reverse mutagenesis, and were stable on in vitro and in vivo passage. In the case of lymphotropic viruses (DEN), no mutations were required to achieve an attenuated vaccine candidate. ChimeriVax™-JE and -DEN-2 vaccines were tested for attenuation, immunogenicity and protective efficacy in monkeys. The vaccines were more attenuated than YF 17D vaccine. Monkeys given doses as low as 2 log₁₀ PFU developed high neutralizing antibody titers and were fully protected against intracerebral (JE) or subcutaneous (DEN-2) challenge with wild-type viruses. Prior YF immunity did not preclude successful vaccination. ChimeriVax™-JE virus was markedly restricted in its ability to replicate in mosquitoes. Because of its long history of use in humans, YF 17D is an ideal gene vector. Replacement of the YF E gene avoids problems of anti-vector immunity associated with other live vectors.

S19 Booster doses of measles vaccine in schoolchildren: responses to different vaccine strains and the aerosol route
A. Dilraj¹, F.T. Cutts², J.F. de Castro³, J.G. Wheeler², D. Brown⁴, C. Roth⁴, H.M. Coovadia⁵, J.V. Bennett⁶. ¹Medical Research Council, Durban, South Africa; ²Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London; ³Mexican Ministry of Health, Mexico City; ⁴Enteric and Respiratory Virus Laboratory, Public Health Laboratory Service, London; ⁵Department of Paediatrics and Child Health, University of Natal, Durban; ⁶Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta.

The administration of more than one dose of measles vaccine is necessary for the sustained control of measles. Although historical data suggest that the aerosol route might be more immunogenic for booster doses than traditional subcutaneous injections, there have been no randomized comparative trials.

Schoolchildren (5-14 years) were assigned by block randomization of classes to receive standard titer doses of either Schwarz or Edmonston-Zagreb (EZ) measles vaccines subcutaneously or by aerosol. 82% had histories of previous vaccination. Blood samples for antibody assay were collected prevaccination, at 1 month and 1 year postvaccination.

Among 992 children who had antibody titer data available for all time-points, the serological response to EZ vaccine by aerosol was significantly better at 1 month and 1 year than to any of the other vaccine groups. Among children who received EZ vaccine by aerosol, only 4% were seronegative 1 year post-vaccination, significantly fewer than the 9% of the EZ subcutaneous group and 14% of the Schwarz subcutaneous group. The response to subcutaneously administered EZ vaccine was also better than to Schwarz subcutaneously. The Schwarz aerosol group performed poorly, as its reconstituted vaccine lost potency quickly in the nebulizer.

The aerosol route using present devices and a suitably stable vaccine is effective and acceptable. It is readily adaptable to mass campaigns, avoiding the risks of unsafe injection practices, and could significantly abet measles elimination/eradication efforts.

S18 Effectiveness of inactivated Hantaan virus vaccine(Hantavax[®]) against hemorrhagic fever with renal syndrome: a population-based, case-control study in Korean soldiers

You-Choel Shin¹, Eunil Lee¹, Yong-Tae Yeom¹, Luk-Ju Baik², Seung-Chul Park², Sang-Hoon Kim³, Min-Ja Kim³
Department of Preventive Medicine¹, Microbiology², and Internal Medicine, Korea University College of Medicine, Seoul, Korea, Ministry of National Defense of Korea³

In Korea hemorrhagic fever with renal syndrome(HFRS) is a serious health problem. Formalin inactivated mouse brain-derived Hantaan virus vaccine(Hantavax[®]) was developed and licensed in 1990. However, the efficacy of the vaccine has not been proven in a randomized field trial because cases of HFRS continue to decline since the vaccine was recommended for use by the health authority. To evaluate the effectiveness of Hantavax[®], we performed a case-control study among Korean young soldiers known as the high risk group. Study subjects were 27 cases and 833 controls. Cases were identified from January 1997 through December, 1998, and confirmed by clinical and serologic data. 833 controls were healthy soldiers surveyed at the patients' military units. Vaccination histories were obtained through questionnaire. With unconditional logistic regression analysis the vaccine effectiveness is 90.7% (95% confidence interval[CI], 56-99.5%). When conditional logistic regression analysis is performed for 1:4 matched data, the effectiveness is 93% (95% CI, 40.4-99.2%). Effect of potential confounding variables on the results was negligible. We conclude that the inactivated Hantaan virus vaccine is effective in preventing HFRS. Further study is ongoing, including newly identified cases.

S20 Reactogenicity and immunogenicity of combined measles-mumps-rubella-varicella vaccine, and of measles-mumps-rubella vaccine alone or with varicella vaccine as a single injection extemporaneous mix.

*T. Nolan¹, P. McIntyre², D. Robertson³, G. Hogg⁴, D. Descamps⁵. ¹Royal Children's Hospital, Melbourne; ²New Children's Hospital, Sydney; ³Women's & Children's Hospital, Adelaide; Australia; ⁴SmithKline Beecham Biologicals, Rixensart, Belgium.

A tetravalent measles-mumps-rubella-varicella vaccine (MMR-V) would facilitate implementation of varicella vaccination into routine childhood schedules.

Objective: Assess immunogenicity/reactogenicity of MMR & monovalent varicella (V) vaccine (G1) as an extemporaneous mix and MMR-V (G2) compared to MMR (G3).

Method: 240 healthy children aged 12 months in 3 groups of 80 of whom 238 completed the study, with no dropouts due to serious adverse events. Vaccines (SmithKline Beecham Biologicals) - live attenuated measles (Schwarz strain, $\geq 10^{3.7}$ CCID₅₀), mumps (RIT 4385 strain, $\geq 10^{4.7}$ CCID₅₀), rubella (RA 27/3 strain, $\geq 10^{5.8}$ CCID₅₀), varicella (Oka strain, $\geq 10^{3.5}$ pfu/vial) vaccine as MMR-V, MMR or V stored at 2-8°C and given as single 0.5mL s.c. dose.

Results: There were no significant differences between groups in rates of fever, pain, redness, or swelling, nor significant differences in seroconversion rates (S+ = seropositive). For GMTs 60 days post-vaccination - measles: p=.004 G1>G3, G2>G3; mumps: p=.95; rubella: p=.027 G3>G2, varicella: p=.008 G1>G2.

| Antibody | S+ cut-off | MMR & V (G1) | | MMR-V (G2) | | MMR (G3) | |
|-----------|------------|--------------|--------|------------|--------|----------|--------|
| | | % S+ | GMT | % S+ | GMT | % S+ | GMT |
| Measles | 150 mIU/mL | 91.9 | 2509.7 | 98.6 | 2964.9 | 97.2 | 1627.0 |
| Mumps | 231 U/mL | 94.5 | 1170.5 | 97.2 | 1212.5 | 98.6 | 1164.3 |
| Rubella | 4 IU/mL | 100.0 | 64.5 | 98.6 | 57.3 | 100.0 | 80.4 |
| Varicella | 1:4 | 95.9 | 96.6 | 93.2 | 53.9 | - | - |

Conclusion: This MMR-V vaccine and the extemporaneous mix demonstrated similar reactogenicity and seroconversion rates to MMR alone.