

## **THE CHALLENGE OF DEVELOPING AN MMR-VVV COMBINATION VACCINE**

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In the late 1960's, Measles, Mumps and Rubella vaccines were been melded into an effective combination known generically as "MMR" vaccines. These vaccines have immunological and clinical performance equal to that of their monovalent components plus the practical advantage of single-shot administration. The addition of varicella to make an "MMRV" vaccine has been the goal of several laboratories since the early 1980's. Numerous studies have shown that when a monovalent dose of varicella vaccine is added to an MMR vaccine the titer of antibody against varicella is reduced by about one-half. This is believed to be due to immunological interference by the measles vaccine. We have developed a validated clinical correlate of protection from "breakthrough" varicella disease, the gpELISA assay. A low titer of antibody to varicella by gpELISA 6 weeks past-vaccination predicts a higher breakthrough rate. Therefore, we would not accept an MMRV vaccine with diminished varicella immunogenicity. We have recently overcome this interference problem by increasing the dose of varicella vaccine virus in the MMRV mixture. The resulting MMRV vaccine remains well-tolerated and should provide, in a single administration, clinical protection from varicella disease equivalent to that provided by MMR and varicella vaccines administered separately. A key element of this success may be the genetic composition of the viruses in this mixture.