Title **–** Evaluating the Compatibility of Three Aluminum Salt-Adjuvanted Recombinant Protein Antigens (Trivalent NRRV) Combined with a Mock Trivalent Sabin-IPV Vaccine: Analytical and Formulation Challenges

Author List **–** Prashant Kumar, Atsushi Hamana, Christopher Bird, Brandy Dotson, Soraia Saleh-Birdjandi, David B. Volkin and Sangeeta B. Joshi

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Manuscript Abstract **–** In this work, we describe compatibility assessments of a recombinant, trivalent non-replicating rotavirus vaccine (t-NRRV) candidate with a mock trivalent Sabin inactivated polio vaccine (t-sIPV). Both t-sIPV and t-NRRV are incompatible with thimerosal (TH), a preservative commonly used in pediatric pentavalent combination vaccines (DTwP-Hib-HepB) distributed in low- and middle-income countries (LMICs), preventing the development of a heptavalent combination. The compatibility of t-NRRV with a mock DTwP-Hib-HepB formulation is described in a companion paper. This case study highlights the analytical and formulation challenges encountered when combining a mock t-sIPV vaccine (unadjuvanted) with Alhydrogel® (AH) adjuvanted t-NRRV. Selective and stability-indicating competition ELISAs were implemented to monitor antibody binding to each of the six antigens (±AH). Simple mixing caused the undesired desorption of t-NRRV from AH with the concomitant binding of t-sIPV to AH. Although the former effect was mitigated by dialyzing sIPV bulks, decreased sIPV storage stability was observed at accelerated temperatures in the bivalent combination with a rank-ordering of P[8]>P[6]>P[4] and sIPV3>sIPV2>sIPV1. The compatibility of AH-adsorbed t-sIPV with alternative preservatives was evaluated, and parabens (methyl, propyl) were identified for potential use in this multi-dose bivalent formulation. Along with a companion paper, the lessons learned are discussed to facilitate the future formulation development of pediatric combination vaccines with new antigens.

Keywords **–** pediatric combination vaccine**;** non-replicating rotavirus vaccine; Sabin inactivated polio vaccine; formulation; compatibility; stability; preservatives; adjuvant; ELISA