

**S25** Effect of Aging on Immune Response to Vaccines: Lessons from Animal Models

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Influenza is a leading cause of morbidity and mortality in older persons. The current influenza vaccine is only modestly successful, because of an age-related decline in immunogenicity and induction of type-specific serum IgG antibody. Studies over the past 10 years on the effects of age on pathogenesis of influenza have shown that following influenza challenge, aged mice have a more severe illness, characterized by delayed recovery and increased propensity of the virus to spread from the nose to the lungs. The primary immunological mechanism is an age-related loss of anti-influenza CD8+ cytotoxic T-lymphocyte (CTL) activity. Aged mice also have lower Th1-cytokine response and a decline in heterotypic immunity. To overcome these shortcomings, we have been evaluating DNA-based vaccines. In experiments using plasmid DNA encoding influenza A/PR8/34 hemagglutinin (HA) and nucleoprotein (NP), or a replication-deficient recombinant vaccinia virus, we found that aged mice developed slightly lower serum anti-HA antibody response, but CTL activity similar to young animals. Challenge experiments showed that the aged animals immunized by either method were protected from a homotypic challenge, but had only partial protection from a heterotypic challenge. We have also found that the replication-deficient recombinant vaccinia virus is immunogenic in pigs and horses. These data demonstrate that DNA-based vaccines are immunogenic in young and aged animals and suggest that they may be beneficial in older persons.

**S26** The Challenge to Immunization Practice by Increasing Numbers of Parenteral Vaccines

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The biotechnology revolution is producing a growing bounty of new vaccines that challenge their incorporation into an already complex childhood immunization schedule. The minimum number of injections from birth through 16 years of age in the U.S. increased from 8 in 1989 to 14 in 1998. At a single visit in the second year, three to four injections may be required, which >40% of physicians and parents are reluctant to administer, leading to costly additional visits, missed vaccination, and increased disease burden. Needles/syringes also may transmit disease through needlestick injuries and improper reuse in many countries, and may be impractical for global measles eradication.

Combination vaccines may be but a short-term solution, as they are expensive to document chemical compatibility and immunologic noninterference, and tend to encourage concentration in the vaccine industry. In the medium-term, a new generation of safer, needle-free parenteral injection devices may overcome pain by allowing reduction of volume and/or dose, or perhaps deliver multiple vaccines through parallel channels in a "single painful event". Oral and intranasal vaccines represent a long-term solution to the new vaccines challenge.

**S27** Induction of Immune Responses Following Mucosal Administration of Vaccine Antigens

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The concept of common mucosal immune system is based on the observations that exposure of replicating or non-replicating infectious agents and other antigens to the lymphoid tissue in the nasopharynx (NALT), broncho epithelium (BALT) or Peyer's patches and gut (GALT) results in the development of specific mucosal and cellular immune responses in these sites, as well as, in other distant mucosal surfaces, as a result of preferential migration, systemic circulation and eventual seeding and local proliferation of antigen sensitized cells in the mucosal epithelium and lamina propria. The nature and extent of systemic immune responses after mucosal immunization is significantly influenced by the biologic characteristics of the vaccine antigens, adjuvants and vehicles employed for antigen delivery. Recent studies have also shown that many replicating agents interact specifically with mucosal epithelium and induce synthesis of a variety of immunoregulatory and proinflammatory cytokines and chemokines and activation of T-cell subsets T-1 and T-2. It is apparent that introduction of microbial antigens via the mucosal surfaces induce effective mucosal and systemic immunologic responses and provide significant immunity against subsequent reinfection. The systemic immune responses to soluble proteins and possibly autoantigens can, however, be manipulated under appropriate conditions via mucosal immunization to induce systemic hyporesponsiveness (oral tolerance).

**S28** Efficacy of a Trivalent Live Attenuated Intranasal Influenza Vaccine in Children

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One-thousand six-hundred two children participated in a randomized double-blind efficacy study of a trivalent cold adapted live attenuated influenza vaccine given by nasal spray. Children age 15 to 72 months were randomized to receive either two doses of vaccine or placebo (1,314 children) or one dose of vaccine or placebo (288 children). Immunogenicity studies were performed in a subset of 194 children. Prior to vaccination, many children were seronegative (HAI≤1:4) to the viruses in the vaccine (H3=47%, B=67%, H1=67%). The vaccine was safe and well tolerated. One dose of vaccine stimulated a four-fold antibody rise to H3 (92%), B (88%) and H1 (16%) among seronegative children, and these rates increased to 96%, 96% and 61%, respectively, after Dose 2. During the 1996-97 winter season, 3,127 episodes of disease were detected and cultured for influenza viruses. One hundred nine children had 115 cases of culture positive influenza: 71 were caused by influenza A (H3) and 44 by influenza B viruses. The overall efficacy for prevention of influenza was 93% (95% CI=87-96%). The efficacy against influenza A/H3N2 was 95% (95% CI=88-97%) and the efficacy against influenza B was 91% (95% CI=79-96%). A single dose also was efficacious against the two outbreak strains; one dose efficacy against influenza A/H3N2 or B was 89% (95% CI=64-96%); one dose efficacy against influenza A/H3N2 was 87% (95% CI=47-97%) and against influenza B was 91% (95% CI=46-99%). The ease of administration, safety and high efficacy make this vaccine suitable for use in children to prevent influenza.