[S4-1] [10/17/2002(Thur) 14:00-14:25/Hall B]

Intranasal Vaccination with Conjugate Vaccines Protects Against Invasive Disease Caused by Encapsulated Bacteria entering the Body Via the Respiratory Mucosa.

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Streptococcus pneumoniae, Haemophilus influenzae and *Neisseria meningitidis* are encapsulated bacteria which encounter the respiratory mucosa and cause nasopharyngeal carriage that may lead to mild mucosal infections or severe invasive disease.

Host defenses depend largely on antibodies to the polysaccharide capsule, which mediate compliment dependent opsonophagocytosis and/or lysis. IgG and IgA antibodies may also inhibit colonization at mucosal surfaces and thereby decrease the risk for infection and reduce transmission. Polysaccharides (PS) are not immunogenic in infants and young children, but several PS-protein conjugate vaccines have proven immunogenic and highly efficaceous aganist invasive disease in infants.

Immunization with pneumococcal conjugate vaccines (PNC) elicits protective immunity in an adult murine model of pneumococcal infections caused by intranasal challenge, the natural route of infection. Since pneumococcus is a respiratory pathogen, mucosal immune responses may play a significant role. Mucosal vaccination has the advantage of inducing both mucosal and systemic immune responses, but mucosal immunization with inactivated vaccines usually requires adjuvants. Pneumococcal conjugate vaccines administered intranasally with mucosal adjuvants, such as glyceride based formulations (Rhinovax) or the non-toxic LT-K63 or LT-R72 mutants of *E. coli* heat-labile enterotoxin, elicit enhanced systemic IgG and IgA antibodies, as well as mucosal IgA. Protection against bacteremia and lung infection is obtained and the pneumococcal density in blood and lungs correlates with serum levels of IgG antibodies to the polysaccharide capsule. Mucosal immunization with PNC and the non-toxic LT-mutants also increases survival from lethal pneumococcal disease. Protective efficacy has been demonstrated for pneumococcal conjugate vaccines of several serotypes administrated with several adjuvant

formulations.

In early infancy bacterial vaccines elicit IgG responses that are delayed, weak and shortlived. In addition, the poor immunogenicity of PS antigens in the very young may be related to low expression of complement receptor 2 on B cells and immaturity of marginal zone B cells, which are considered to be crucial in antibody response to PS antigens. However, conjugate vaccines have proven immunogenic in early infancy. The intranasal pneumococcal infection model was adapted to early life in order to design optimal vaccination strategies for neonatal vaccination against encapsulated bacteria. Immunogenicity and protective immunity of pneumococcal conjugate vaccines has been assessed in 3 weeks old and 1 week old mice, which best correspond to the state of immune maturation of human infants and newborns, respectively. Both infant and neonatal mice can mount PPS-specific antibody responses, although these remain lower than in adult mice. Accordingly, protective efficacy against bacteremia and lung infection is also impaired, compared to that observed in adult mice. PPS specific IgG responses and protective efficacy can be enhanced in the young mice by coadministration of the non-toxic LT-K63 adjuvant and PNC, either s.c. or i.n. Mucosal immunization is particularly efficient in neonates, eliciting higher antibody levels and better protective efficacy against pneumococcal infections than parenteral immunization using the same conjugate vaccine and adjuvant. In addition, i.n. immunization induces vigorous salivary IgA response, which may affect nasopharyngeal colonization and reduce transmission and improve protection against mucosal infections, like otitis media.

These results suggest that mucosal immunization with conjugate vaccines and novel adjuvants may be able to circumvent some of the limitations of neonatal antibody responses which are required for protective immunity against encapsulated bacteria in early life.

Financial support: The Icelandic Research Council, The Research Fund of University of Iceland and European Community (QLK2-CT-1999-00429, Neovac-EC).