Bacterial polysaccharide–protein conjugate vaccines

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Following demonstration that chemical conjugation of polysaccharide antigens to proteins could enhance their immunogenicity in the 1920s, interest in this approach to primary prevention of bacterial infections waned with the development and widespread use of antibiotics. Emergence of resistant bacteria rekindled interest in the late 20th century, which saw extremely rapid development and implementation of several vaccines which are already rapidly changing the epidemiology of childhood infections with *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis*. Others such as Group B streptococcus and *Salmonella typhi* infections may soon follow. However, several important questions about the immunology of these antigens remain unanswered and the long-term implications of reducing or eliminating the circulation of organisms which are more commonly nasopharyngeal commensals than pathogenic invaders are uncertain.

Introduction

Young children are prone to infections. There are now abundant data that this reflects not only their immunological naïvety, but also a degree of immunoincompetence relative to older children and adults. No doubt, to some extent structural immaturity, such as fragility of integument and mucosae, also contributes. There is a large published literature comparing, in infants and older individuals, the size or function of almost every element of immunity, cellular and humoral, innate and adaptive; studies which often demonstrate the former to be the weaker[1]. It is hard to know what to make of much of this observational information, but in some instances the implications are clear. Adaptive cell mediated immune responses to a wide variety of foreign microbial antigens in newborns are both weaker and slower than in older children. Since all the necessary components for functional responses appear to be in place well before term[2], perhaps this

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incapacity reflects a post natal lag period in immunological regulation, still set to tolerate foreign (maternal) antigens while living in the (normally) sterile environment of the uterus.

If this supposition is true, it remains puzzling that a more rapid post natal immunological 'reboot' has not evolved, as this relative refractoriness often appears to persist for months, at least for some aspects of specific antimicrobial immunity. Interference by transplacentally acquired IgG—a vital element of immune protection against infection during early life, which disappears with a half-life of approximately 28 days after delivery—can to some extent account for the persistent suppression of antibody responses—particularly to protein antigens—but does not cause the down regulation of T cell function[3]. Nor does maternal antibody explain the profound and long lasting failure of infants to make antibodies to the polysaccharide (PS) capsular antigens which decorate many bacterial pathogens[4], a failure which is presumably at least partly responsible for the high incidence of invasive infections due to these organisms in this age group.

Antibody responses to PS antigens are the subject of considerable modern myth. Since they are not peptides, PSs should not, by definition, be processed and presented by MHC class II antigens, so that the recruitment of T cell help by this route for B cell function is not expected. Nevertheless, isotype switching does occur—not only IgM but also abundant IgG and particularly IgA responses to these antigens are seen[5,6]. It appears that a distinct signalling pathway may regulate this important antibody response pathway[7] whose size and character vary not only between individuals[8] and with age, but also with previous exposure[9] and between antigens.

Complete and permanent tolerance to some bacterial capsular PS antigens is the rule. For example, Lancefield Group A streptococci (*Streptococcus pyogenes*) colonizing the nasopharynx, an important cause of both mucosal and invasive disease in children, are consistently encapsulated, although to a variable extent. However, the PS in question is hyaluronic acid—an antigen against which antibody responses would be unwanted as it is a major component of human connective tissues[10]. The capsule of *Neisseria meningitidis* group B is likewise poorly immunogenic as a vaccine[11], an observation which may be explained, at least in part, by the structural similarity of the capsular PS with polysialic acid moieties which decorate components of mammalian tissues including the central nervous system[12].

Nevertheless, the PS capsular antigens of many other pathogenic bacteria do induce substantial protective serum antibody responses when used as vaccines. However, for most of these antigens, this is not true in young children. Although the age of 2 years is often cited as that at which such responses start to be seen, in fact the doses of these antigens needed to elicit protective responses and the average age at which such responses become active vary quite substantially and predictably between antigens. For example pneumococcus type 3 capsular PS is relatively immunogenic in infants whereas types 6A and 6B are extremely poor immunogens, with other types ranging in between[13].

One is left wondering exactly why this is so. Presumably it is no accident. This implies some relative survival advantage of this temporary anergy, perhaps less marked than for the fully 'invisible' antigens described above, but operative nonetheless. On the other hand, it is also possible that the encapsulated bacteria that infect human children today may not have been around long enough in evolutionary time for the survival advantage of vigorous early immune responses to their capsules yet to have taken effect.

In any case, faced with the real problem of the serious morbidity of these infections in young children and evidence that serum antibodies to capsular antigens protect, such theoretical considerations have taken second place to efforts to render these antigens immunogenic in this high risk group. The principle that made this possible was established over 70 years ago with the first description of an effective bacterial PS protein conjugate vaccine[14]. Covalent conjugation of PS haptens to protein carriers renders them capable of inducing humoral immune responses with the characteristics of T cell dependent antigens: responses with memory, affinity maturation and, critically, immunogenicity in young children. A conceptual schema for this, as most usually expounded, is depicted in Figure 1, which combines the afferent functions of antigen recognition and presentation and the efferent function of antibody production and release into a single B cell for simplicity's sake.

There is a tendency to focus on the effects of age and antigen on immune responses and ignore the heterogeneity that exists between individuals. Every geometric mean titre disguises a population whose antibody responses to a standard vaccine dose regimen vary over at least one, and often more than two orders of magnitude and among whom there are always some who make no detectable response at all. The genetic allotypes which doubtless underlie this heterogeneity between individuals (and racial groups) remain incompletely understood[15] and may be distinct for T-independent and T-dependent regulation of antibody responses in some cases[16] but not others[8]. The current 'one size fits all' approach to immunization may be the only workable one at present but perhaps, one day, we will designate immunization regimens not by national boundaries, but also design them for each individual recipient. Meantime, it is worth remembering that vaccine immunogenicity and efficacy findings in one group cannot necessarily be extrapolated to others whose genetic characteristics are distinct.