

## Capsular Polysaccharide Vaccines Today

**Summary:** Polysaccharide (PS) vaccines are a relatively new class of antibacterial vaccines that have special advantages but also special problems related to their character. Several of them have proven very effective in preventing bacteremic infections caused by encapsulated bacteria such as meningococci, pneumococci and *Haemophilus influenzae* type b. Protective activity shows excellent correlation with serum anti-PS. However, young children often respond poorly to PS antigens and this limits the use of these vaccines in childhood. Some PS are poor immunizing agents even in adults. The practical implications of these aspects for the use and development of PS vaccines are discussed.

**Zusammenfassung:** Kapsel-Polysaccharid-Vakzinen heute. Polysaccharid (PS)-Vakzinen sind eine relativ neue Klasse von Impfstoffen, die besondere Vorteile, aber auch ganz spezielle Probleme aufweisen. Mehrere dieser Impfstoffe haben sich als sehr wirksam zur Prävention bakteriämischer Infektionen durch Kapselbakterien wie Meningokokken, Pneumokokken und *Haemophilus influenzae* Typ b erwiesen. Die protektive Wirkung korreliert hervorragend mit dem anti-PS im Serum. Junge Kinder reagieren jedoch oft nur schwach auf PS-Antigene, was der Anwendung dieser Impfstoffe in der Kindheit Grenzen setzt. Einige PS sind auch bei Erwachsenen nur gering immunogen. Die praktischen Folgerungen hieraus für die Anwendung und Entwicklung der PS-Vakzinen werden diskutiert.

### Introduction

In the last 15 years, capsular polysaccharide (PS) vaccines have proven efficacious and useful in affording protection against bacterial meningitis as well as against other invasive, that is bacteremic, infections caused by the same bacteria. While our understanding of these vaccines and their mode of action has increased, we have also learned that they have certain limitations, because of which they are not a panacea for all of these diseases. Briefly, we now have good PS vaccines against meningococci of all serogroups other than B and for most serotypes/groups of pneumococci that cause invasive infections. The efficacy of the PS vaccine against *Haemophilus influenzae* type b is limited by the age of the child to be vaccinated, but it could, when used at the proper age, prevent half of all serious infections caused by *H. influenzae* type b.

Capsular PS vaccines are generally very well tolerated. Whereas some early preparations contained endotoxin and could cause transient fever reactions, especially in infants, this problem could be eliminated as soon as it was realized (1). The pneumococcal vaccine can cause adverse reactions by a different mechanism, a local antigen-antibody reaction at the site of the PS injection (2). This is all the more likely the more anti-pneumococcal antibodies the person has – meaning that the vaccination was not necessary in the first place. In practice this means that too frequent revaccination is not recommended – but in persons who need it because of reduced antibody response for one reason or another, revaccination is of course all right exactly for this reason.

There is an excellent correlation between the concentration of serum antibodies to the capsular PS and protection from invasive infection (3–5). A very good example of such a correlation is seen in *H. influenzae* type b infections. 50 years ago, serum anti-*H. influenzae* type b bactericidal activity was already shown to be inversely correlated with the occurrence of bacteremic *H. influenzae* type b infection at different ages (6). The bulk of the bactericidal activity is due to antibodies to the capsular PS, and indeed the same correlation can be seen when comparing the occurrence of the disease with the mean serum concentration of anti-*H. influenzae* type b PS antibodies (3). This correlation is of great practical importance since it allows PS vaccines to be tested in relatively small groups of people; if they stimulate a good serum antibody response, they are likely to be protective. Thus it is possible to monitor the quality of such vaccine preparations and the probable duration of protective immunity in a relatively easy way.

### Special Properties of Polysaccharides as Immunizing Agents

Several capsular PS have proven good immunizing agents in man (7, 8). This is actually surprising since the same preparations are often not at all or only poorly immunogenic in the common experimental animals. The same animals can usually respond to the PS antigens if the vaccine is not purified PS but whole bacteria containing this PS in their capsules, or the PS conjugated to a protein carrier (9, 10). Why humans respond better to the purified PS antigens is not known. The PS antigens differ from the more

Prof. P. H. Mäkelä, M.D., National Public Health Institute, Mannerheimintie 166, SF-00280 Helsinki 28.

familiar protein antigens – tetanus or diphtheria toxoids, and the major immunizing components of most viral vaccines – in important ways. One dose of vaccine is enough to produce the maximal antibody response, and the response cannot, as a rule, be boosted with further doses. The elevated serum antibody concentrations can last for a very long time, but this depends both on the PS and the age of the person vaccinated. Finally, most people have antibodies to many PS antigens. Thus, the antibody response to vaccination is not a true seroconversion from an antibody-negative to an antibody-positive state, but rather an increase of the antibody concentration to a level sufficient to protect from infection (the “natural” antibodies are protective, too, if present at a high enough level; the relatively strong resistance of adults to bacterial meningitis is very probably due to them). The adult level of anti-PS antibodies develops throughout infancy and childhood, presumably in response to contacts with bacteria containing the same or related, cross-reactive PS antigens. In many cases vaccination can speed up this process of natural immunity development and thus extend the infection resistance to an earlier age.

Thus, the advantages of PS vaccines are many. However, there is another side to the coin, represented by the limitations to their applicability. These are all related to the immunizing capacity of the PS. Whereas adults usually respond with a high antibody level that is sustained for a long time, ten years or more, the response of children tends to be limited both in height and persistence (11, 12). Thus, the duration of protection will depend on the age when the child was vaccinated. Secondly, some PS may be good immunogens in the adult but almost totally without effect in infants and young children (3). Thirdly, some PS may immunize poorly, even in adults. This biological mechanisms dictating these limitations are not well understood. A predominant stimulation of suppressor cells is one possibility, antigenic relatedness to PS structures in the human tissues causing immunological tolerance is another one (13, 14). It would, however, be important to understand the basis of these limitations in order to direct future research towards improved vaccines in a rational manner.

### Meningococcal Vaccines

The meningococcal vaccine now recommended for use is the tetravalent one, containing PS of groups A, C, Y and W135. Since serious infections caused by groups Y or W135 are quite rare, it is also usually acceptable to use the A + C vaccine. All these PS cause good antibody response when given to adults or children older than two years, but in younger children only the group A (meningococcus A) vaccine gives a satisfactory response. It has, however, been shown to be protective starting from three months of age (4); it is also one of the few PS that show a booster response when reinjected two to six months after the first dose (4, 12).

The elevated antibody levels and protection can last quite a long time: protection afforded by the meningococcus A vaccine was shown to last for more than 5 years in Finland in a postepidemic situation when the incidence of group A disease was low (15). The elevated anti-meningococcus A antibody levels were estimated to last for ten years in persons vaccinated at the age of seven years or more (12). Their rate of decline was progressively more rapid in younger children, and thus it would be advisable to give a second dose of vaccine two to three years after the first to children who are younger than five years when first vaccinated.

The most rational use of the tetravalent meningococcal vaccine would be to give it to all children at the age of two to three years, with a second dose two years later. Even if the incidence of the respective meningococcal infections in most industrialized countries is rather low, this practice would have the definitive advantage of inducing in the population a solid immunity status that would most probably prevent any meningococcal epidemics. However, in areas where meningococcal epidemics are frequent and the incidence very high – such as is the case, for example, in the Sahel area in Africa – this practice would be of special importance. Unfortunately, these areas have so far mostly found it difficult to organize such continued vaccination. Instead, they tend to use the meningococcal vaccine when an epidemic has already started, in order to stop it quickly. It is obvious that this is not as effective as a community-wide protective immunization.

At special risk of meningococcal meningitis are two groups of people: close contacts (family members) of meningococcal patients, and recruits in the army. It is obvious that such risk groups should be immunized. The vaccination of the family members should be arranged by the doctor who diagnosed the initial case, and it should be performed as soon as possible and without waiting, for example, for confirmation of the meningococcal group in the patient. In this case of special risk, vaccine should also be given to infants younger than two years, who do benefit at least from the group A component.

The tetravalent meningococcal vaccine is a good agent against meningococcal epidemics. In non-epidemic periods, however, most cases are caused by group B meningococci, for which the present vaccine affords no protection. All attempts at producing a vaccine from the PS of group B have been futile. The recent demonstration of structures in the human brain that cross-react with antibodies to the group B PS suggests that there is a good basis for immunological tolerance to this PS. Alternative vaccines, based on other surface structures of the meningococci, are being explored, but so far we have no group B vaccine that has shown a protective effect in man (16, 17).

### Haemophilus influenzae

Almost all cases of invasive *H. influenzae* infection – be it meningitis, epiglottitis, arthritis, pneumonia or septic-

mia – are caused by type b bacteria whose capsular PS is a ribosyl-ribitol-phosphate polymer. This *H. influenzae* type b polysaccharide gives rise to good protective immunity in children vaccinated when 18 months-old (3). It was, however, without effect in infants and younger children.

Since *H. influenzae* type b meningitis peaks between six and 18 months of age, much work has been devoted to improving the immunogenicity of the PS in order to extend the protective efficacy to a younger age. This may be difficult, since even natural *H. influenzae* type b infection, including meningitis, does not give rise to an anti-*H. influenzae* type b response in children younger than 18 months (18). The most promising approach may be covalent conjugation of the *H. influenzae* type b PS to a protein carrier (10). This is expected to change the PS to a more protein-like immunogen, that would give rise to a response of IgG antibodies that could be boosted. However, the first tests of the immunizing ability of this PS in human infants are only now being done. If they prove promising, a field trial will probably still be necessary to establish protection. Furthermore, such chemically modified vaccines have so far not been used in man, and therefore the potential vaccine will have to undergo quite extensive testing for safety. Thus, even in the most optimistic case, it will take several years before we can plan on a general use of *H. influenzae* type b vaccine in young infants.

In contrast, the *H. influenzae* type b PS vaccine is ready for use in older children. It is protective and safe. Furthermore, a four-year follow-up of children vaccinated with it at ages ranging from three months (when it was not protective) to five years of age showed that it had no untoward late effects (19). Most importantly, there was no indication of immunological tolerance, even in the infants who were too young to respond to the vaccine (20). The administration of this PC vaccine to children at 18 months of age, followed by a second dose two years later, could prevent more than half of all serious *H. influenzae* type b infections (19). It would be cost-effective in the short-run in terms of the costs of hospitalization of the acute cases (3), but its main impact would be in preventing the neurological and psychological sequelae that are common after bacterial meningitis (21).

#### **Pneumococcal Vaccine**

The protective efficacy of PS vaccines against pneumococcal pneumonia was established in man 40 years ago (22). It is most likely that protection from meningitis would be equally good. The pneumococci causing such serious infections can be of many different serotypes/groups, and therefore vaccine development is aimed at a polyvalent vaccine containing capsular PS of all the common types. Until recently, a 14-valent vaccine has been available that covers 80% of all pneumococci isolated from infections (23). A new 23-valent formulation that has an even better coverage is now being introduced and is the vaccine of choice (24).

In industrialized countries, pneumococcal meningitis is rather rare, and vaccination to prevent it might not be justifiable. However, the fact that the same vaccine would prevent pneumococcal pneumonia, which is much more common, changes the situation completely. Pneumococcal pneumonia is most serious in elderly people (who also have an increased risk of pneumococcal meningitis), and vaccination is recommended for all people aged 65 or over. Revaccination should be considered ten years later. Persons at a very high, special risk of serious pneumococcal infections are all those with defective spleen function – primarily those splenectomized – and it is very important that they should all receive the vaccine. In these patients the antibody response is also partially affected, and therefore their serum antibody levels decline more rapidly than normal (25). For this reason it may be useful to revaccinate these patients sooner than normally recommended. The optimal interval is still being investigated; it may be three or five years. In contrast, immunocompromised patients who also have an increased risk of pneumococcal (as well as of other) infections have less benefit from the pneumococcal vaccine because of their poor ability to respond with antibody production (5).

In many developing countries, pneumococcal meningitis, like other serious pneumococcal infections, are much more common. In such a setting, the vaccine given at two years of age, combined with revaccination some years later, would be of great benefit. Unfortunately, the vaccine is quite expensive for this purpose.

The pneumococcal vaccine is not recommended for children younger than two years. This is because several of its components, especially those of serogroups 6 and 23, immunize very poorly in young children (26). The situation looks rather similar to that with the *H. influenzae* type b PS; it remains to be seen whether similar methods of improving immunogenicity will work for all these.

#### **Neonatal Meningitis**

The bacteria causing meningitis in the newborn are a completely different set from those discussed above. Two bacteria are of prime importance: *Escherichia coli* of the capsular type K1, and streptococci of group B. The K1 capsule is chemically and antigenically identical to that of group B meningococci, and thus no vaccine is available or can readily be found. The group B streptococci are also encapsulated and fall into five capsular serotypes, all with a related chemical structure. Since neonatal meningitis has been shown to occur in the babies of mothers without antibodies to the group B streptococci (27), it would be essential to induce a good response in all mothers. Vaccination trials suggest that these PS may not be able to induce an antibody response in all those vaccinated (28). The logistics of administering vaccine to women before they become pregnant have also not been solved. Thus, the possibilities of preventing neonatal meningitis by vaccination in the near future do not look very good.

Literature

1. Kuronen, T., Peltola, H., Nors, T., Haque, N., Mäkelä, P. H.: Adverse reactions and endotoxin content of polysaccharide vaccines. *Dev. Biol. Stand.* 34 (1977) 117-125.
2. Borgono, J. M., McLean, A. A., Vella, P. P., Woodhour, A. F., Canepa, I., Davidson, W. L., Hilleman, M. R.: Vaccination and re-vaccination with polyvalent pneumococcal polysaccharide vaccines in adults and infants. *Proc. Soc. Exp. Biol. Med.* 157 (1978) 148-154.
3. Peltola, H., Käyhty, H., Sivonen, A., Mäkelä, P. H.: The *Haemophilus* type b capsular polysaccharide vaccine in children. A double-blind field study of 100,000 vaccinees three months to five years of age in Finland. *Pediatrics* 60 (1977) 730-737.
4. Peltola, H., Mäkelä, P. H., Käyhty, H., Jousimies, H., Herva, E., Hällström, K., Sivonen, A., Renkonen, O. V., Pettay, O., Karanko, V., Ahvonen, P., Sarna, S.: Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children three months to five years of age. *N. Engl. J. Med.* 297 (1977) 686-691.
5. Landesman, S. H., Schiffman, G.: Assessment of the antibody response to pneumococcal vaccine in high-risk populations. *Rev. Inf. Dis.* 3 (1981) 184-197.
6. Fothergill, L. D., Wright, J. D.: Influenzal meningitis. The relation of age to the bactericidal power of blood against the causal organism. *J. Immunol.* 24 (1933) 273-284.
7. Gotschlich, E. C., Goldschneider, I., Artenstein, M. S.: Human immunity to the meningococcus. IV. Immunogenicity of group A and group C meningococcal polysaccharides in human volunteers. *J. Exp. Med.* 129 (1969) 1367-1384.
8. Felton, L. D., Prescott, B., Kauffman, G., Ottinger, B.: Pneumococcal antigenic polysaccharide substances from animal tissues. *J. Immunol.* 74 (1955) 205-213.
9. Goebel, W. F.: Studies on antibacterial immunity induced by artificial antigens. II. Immunity to experimental pneumococcal infection with antigens containing saccharides of synthetic origin. *J. Exp. Med.* 72 (1940) 33-48.
10. Schneerson, R., Barbera, O., Sutton, A., Robbins, J. B.: Preparation, characterization, and immunogenicity of *Haemophilus influenzae* type b polysaccharide-protein conjugates. *J. Exp. Med.* 152 (1980) 361-376.
11. Vella, P. P., McLean, A. A., Woodhour, A. F., Weibel, R. E., Hilleman, M. R.: Persistence of pneumococcal antibodies in human subjects following vaccination (40981). *Proc. Soc. Exp. Biol. Med.* 164 (1980) 435-438.
12. Käyhty, H., Karanko, V., Peltola, H., Sarna, S., Mäkelä, P. H.: Serum antibodies to capsular polysaccharide vaccine of group A *Neisseria meningitidis* followed for three years in infants and children. *J. Infect. Dis.* 142 (1980) 861-868.
13. Siskind, G. W., Paterson, P. Y., Thomas, L.: Induction of unresponsiveness and immunity in newborn and adult mice with pneumococcal polysaccharide. *J. Immunol.* 90 (1963) 929-933.
14. Finne, J., Leinonen, M., Mäkelä, P. H.: Antigenic similarities between brain components and bacteria causing meningitis. *Lancet* II (1983) 355-357.
15. Mäkelä, P. H., Käyhty, H., Peltola, H.: Immunity after group A meningococcal polysaccharide vaccine. In: *Danielson, D., Normark, S.* (eds.): Genetics and immunobiology of pathogenic *Neisseria*. Proceedings of an EMBO workshop held at Hemavan, Sweden, June 16-19, 1980, pp. 299-300.
16. Frasch, C. E.: Noncapsular surface antigens of *Neisseria meningitidis*. In: *Weinstein, L., Fields, B. N.* (eds.): Seminars in infectious disease. Vol. 2. Stratton Intercontinental Medical Book Corp., New York 1979, pp. 304-337.
17. Zollinger, W. D., Mandrell, R. E., Griffiss, J. M.: Enhancement of immunologic activity by noncovalent complexing of meningococcal group B polysaccharide and outer membrane proteins. In: *Weinstein, L., Fields, B. N.* (eds.): Seminars in infectious disease. Vol. 2. Stratton Intercontinental Medical Book Corp., New York 1979, pp. 254-262.
18. Käyhty, H., Jousimies-Somer, H., Peltola, H., Mäkelä, P. H.: Antibody response to capsular polysaccharides of groups A and C *Neisseria meningitidis* and *Haemophilus influenzae* type b during bacteremic disease. *J. Infect. Dis.* 143 (1981) 32-41.
19. Peltola, H., Käyhty, H., Virtanen, M., Mäkelä, P. H.: Prevention of *Haemophilus influenzae* type b bacteremic infections with the capsular polysaccharide vaccine. *N. Engl. J. Med.* 310 (1984) 1561-1566.
20. Käyhty, H., Karanko, V., Peltola, H., Mäkelä, P. H.: Serum antibodies after vaccination with *Haemophilus influenzae* type b polysaccharide and responses to reimmunization - no evidence of immunological tolerance or memory. *Pediatrics* (1984) in press.
21. Sell, S. H. W., Merrill, R. E., Doyne, E. O., Zinsky, E. P., jr.: Longterm sequelae of *Haemophilus influenzae* meningitis. *Pediatrics* 49 (1972) 206-211.
22. MacLeod, C. M., Hodges, R. G., Heidelberger, M., Bernhard, W. G.: Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. *J. Exp. Med.* 82 (1945) 445-465.
23. Austrian, R., Douglas, R. M., Schiffman, G., Goetzee, A. M., Koornhof, H. J., Hayden-Smith, S., Reid, R. D. W.: Prevention of pneumococcal pneumonia by vaccination. *Trans. Assoc. Am. Physicians* 89 (1976) 184-194.
24. Robbins, J. B., Austrian, R., Lee, C.-J., Rastogi, S. C., Schiffman, G., Henriksen, J., Mäkelä, P. H., Broome, C. V., Facklam, R. R., Tiesjema, R. H., Parke, J. C., jr.: Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *J. Inf. Dis.* 148 (1983) 1136-1159.
25. Aaberge, I. S., Heier, H. E., Hem, E., Giercksky, K.-E., Groeng, E. C.: IgM and IgG response to pneumococcal polysaccharide vaccine in normal individuals and individuals splenectomized due to trauma. *Acta Pathol. Microbiol. Scand.* [C] 92 (1984) 11-16.
26. Sloyer, J. L., Karr, L. J., Ploussard, J. H., Schiffman, G. D.: Immunologic response to pneumococcal polysaccharide vaccine in infants. *Ann. Otol. Rhinol. Laryngol.* 89, Suppl. 68 (1980) 351-356.
27. Baker, C. J., Kasper, D. L.: Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. *N. Engl. J. Med.* 294 (1976) 753-756.
28. Baker, C. J., Kasper, D. L., Edwards, M. S., Schiffman, G.: Influence of preimmunization antibody on the specificity of the immune response to related polysaccharide antigens. *N. Engl. J. Med.* 303 (1980) 173-178.