Vaccines Against Meningococcal Meningitis: Current Status

Etiologic Agents and the Vaccines

Virulent strains of *Neisseria meningitidis* cause sporadic cases and periodic outbreaks or epidemics of meningitis; the strains that belong to serogroups A, B, and C are responsible for 90% of the cases of meningococcal meningitis in the world. Serogroups B and C are generally associated with the endemic disease, whereas the incidence of serogroup A rises during epidemic periods. Countries such as Cuba, Brazil, Colombia, Chile, Argentina, Uruguay, and the Scandinavian countries recently have experienced increases in serogroup B meningitis, especially in children under five years of age, the group with the highest attack rates.

Polysaccharide-based vaccines proved to confer immunity against serogroups A, C, Y, and W135 in the 1960s (1) and 1970s, and have been available on the market since 1981. Their efficacy was age-dependent: the vaccine for serogroup A confers protection in children over 6 months and the vaccine for serogroup C is not effective in children under two years (2,3). The vaccines for serogroups Y and W135 act in a manner similar to that for serogroup A. Nonetheless, the polysaccharide vaccine for serogroup B is poorly immunogenic and does not protect against the disease. As a result, several alternatives are under study to develop vaccines for this serogroup based on the outer membrane protein of the *N. meningitidis* bacteria, serogroup B, and other surface antigens.

The alternatives under study include development of the serogroup B polysaccharide chemically modified to contain N-propionyl in place of N-acetyl groups coupled to tetanus toxoid (4), the *E. coli* K92 polysaccharide, which cross-reacts with serogroup B when conjugated with tetanus toxoid (5), cloning of the outer membrane protein incorporated into the liposomes, lipopolysaccharides (LPS)-depleted outer membranes or the outer membrane protein of the bacteria. In addition, use of the detoxified lipopolysaccharide or oligosaccharides derived from the LPS (synthetic in some cases) combined with outer membrane protein (OMP), or incorporated into liposomes, is also under study.

In the early 1980s the first vaccines were derived from the outer membrane protein of subgroup B, serotype 2 made of insoluble protein aggregates; they showed low immunogenicity. The more recent vaccines contain outer membrane protein, capsular polysaccharide to maintain solubility of the vaccine, and aluminum hydroxide adjuvant (6).

Efficacy Trials Published to Date

The most recent efficacy trials for several vaccines against meningococcal meningitis are the following:

Walter Reed Army Research Institute, Washington, D.C., USA: Vaccine prepared with the B:15:P1.3 strain, and containing lipopolysaccharide-free outer membrane protein, with serogroup C polysaccharide added, in an aluminum hydroxide adjuvant. The double-blind randomized case-control field trial, was conducted in Iquique, Chile from 1987 to 1989. Two doses of 100 ug protein were administered to 40,000 volunteers aged 1 to 21 years at an interval of 6 weeks. The subjects followed up for 20 months. Overall efficacy was 50%, but protection was age-dependent. Efficacy was 70% in the 5 to 21 year-old age group, whereas no protection was observed in children aged 1 to 4 years (7). Researchers at Walter Reed are continuing their work to develop another generation of the serogroup B vaccine.

National Institute of Public Health, Oslo, Norway: The vaccine contains the outer membrane protein depleted of lipopolysaccharide of the B:15:P1.16 strain, with 3% to 6% high molecular weight protein. It has no capsular meningococcal polysaccharide. To stabilize the protein 3% sucrose was added, and aluminum hydroxide was used as an adjuvant. The vaccine contains class 1, 3, 4, and 5 proteins and was formulated to contain 25 ug of protein per dose; it was administered in two injections at an interval of 6 weeks. The field study, done in 1988, was conducted as a randomized double-blind placebo-controlled trial with youths 13 to 15 years old. Epidemiologic surveillance continued for 29 months; the observed efficacy was 57%. The authors concluded that the vaccine's efficacy is too low to justify its use in vaccination programs (8).

Instituto Carlos Finlay, Cuba: The Cuban vaccine contains the outer membrane from the B:4:P1.15 strain with traces of lipopolysaccharides, polysaccharide from serogroup C, and high molecular weight protein complex. Aluminum hydroxide gel is used as an adjuvant. Each dose contains 50 ug of protein, 50 ug of polysaccharide, and 2 mg of aluminum hydroxide. The randomized double-blind placebo-controlled efficacy trial was conducted in Cuba in 1986-87 among 100,000 schoolchildren (9 to 14 years old). An efficacy of 83% was observed.

A case-control study in São Paulo, Brazil, in which 2.4 million children were vaccinated, demonstrated that the vaccine's efficacy was age-dependent. In children older than 48 months, the efficacy was 74% (confidence interval from 16% to 92%), whereas in children 24 to 47 months old it was 47% (confidence interval -72% to 84%) and in children under 24 months it was -37% (confidence interval less than -100% to 73%) (10).

Reactogenicity of the vaccine: Systemic adverse reactions were mild for all the vaccines studied. Fever, headache, or nausea may occur in up to 10% of persons vaccinated. Local reactions consisting of erythemas, with or without induration and soreness, were recorded in adult volunteers (11,12) but less frequently in children (13).

In Cuba the study of reactogenicity and immunogenicity in children 6 months to 12 years, carried out in 1987, found no significant adverse reactions. The maximum temperature registered among vaccinated groups and those who received the placebo was 37°C or less. The remaining adverse events were erythema and soreness at the point of injection; these were significantly greater in persons who received vaccine than these who received placebo (14).

The analysis of the Norway trial reported only rare and mild adverse reactions (8). None were reported in the Brazil trial (10).

Other Ongoing Studies

In view of the importance of meningococcal meningitis and the current context of scientific and technological development, the World Health Organization's Global Program on Vaccines is supporting a series of research projects that apply complex technologies, such as developing conjugated vaccines, cloning important bacterial proteins, and other technologies, in order to develop more efficacious vaccines for children less than 2 years old (16).

At the request of the Government of Brazil, PAHO's Regional System for Vaccine Development (SIREVA) prepared the Master Plan for the development of an improved vaccine for serogroup B. At present this project includes the participation of three Brazilian institutions: the Instituto Adolfo Lutz and the Instituto Butantan in São Paulo, and Bio-Manguinhos/FIOCRUZ in Rio de Janeiro.

The World Health Organization recently organized a comparative trial, among 400 adolescents, on the immunogenicity and reactogenicity of 2 and 3 doses of the vaccines produced in Norway and Cuba. The trial is under way in Iceland, and is expected to conclude in July of this year.

In Chile, the health ministry undertook another comparative trial on the immunogenicity of these two vaccines, administering them to different age groups, including children under 1 year old and young adults.

The health ministry of Argentina is considering an efficacy trial of the vaccine in the province of Las Pampas.

Conclusions and Relevance for National Immunization Programs

The vaccine produced in Norway is still considered experimental. The vaccine produced at Walter Reed Army Research Laboratory continues to be in the research and development phase. The vaccine produced in Cuba complies with Good Manufacturing Practices and has been registered in several countries of Eastern Europe and Africa, and in some countries of Latin America (Argentina, for use in persons over 4 years; Brazil, where it is registered on a provisional basis; Colombia, registered and licensed; Chile, in process; and Cuba).

Based on the knowledge and published data from the efficacy trials conducted to date, it may be concluded that the vaccine produced in Cuba is efficacious in the over-4-year old group. In one of the trials, low efficacy was observed among children aged 2 to 4 years and little or no efficacy was seen in those under 2 years, the group generally most affected by the disease. However, these trials results are inconclusive and somewhat contradictory. It is crucial therefore that research continue with a view to developing an improved vaccine against serogroup B of meningococcal meningitis, and that the development of case-control efficacy trials continue to determine with certainty, among other things, if the vaccine is efficacious among children under 4 years old.

In those countries or regions that are facing the problems that stem from the increased incidence of meningococcal meningitis, especially of serotype B, it is advisable that the decision to use the vaccine currently available takes into account the available data on attack rates, known age-specific efficacy, and the analysis of the prevalent serogroups and serotypes of *N. meningitidis*, in addition to its age specific cost-benefit.

PAHO is available to any country or subregion that intends to design efficacy trials, to assist in standardizing protocols and to follow up as needed for comparisons with similar studies.

References

1. Gotschlich, EC, Goldschneider I, Artenstein MS. Human Immunity to the Meningococcus IV. Immunogenicity of group A and group C polysaccharides in human volunteers. *J Exp Med* 1969: 129:1367-84.

2. Amato, NV, Finger H, Gotschlich EC, Feldman RA, de Avila CA, Konichi SR, et al. Serologic response to serogroup C meningococcal vaccine in Brazilian preschool children. *Rev Inst Med Trop*. São Paulo 1974; 16:149-53.

3. Taunay AE, Feldman RA, Bastos CO, Galvao PAA, Morais JS, Castro IO. Avaliação do efeito protetor da vacina polissacaridica antimeningococica do Grupo C em Crianças de 6 a 36 meses. *Rev Inst Adolfo Lutz*, 1978: 38:77-82.

4. Jennings HJ, Gamian A, Ashton FE. N-propionylated group B meningococcal polysaccharide mimics a unique epitope on group B *Neisseria menigitidis*. *J Exp Med* 1987: 1207-11.

5. Devi SJN, Robbins JB, Schnefrson R. Antibodies to poly [(2-8)-á-N-acetylneuraminic acid)] and poly[(2-9)-á-N-acetylneuraminica acid)] are elicited by immunization of mice with *Escherichia coli* K92 conjugates: Potential vaccines for Groups B and C meningococci and *E. coli* K1. *Proc Natl Acad Sci USA*. 1991. 88:7175-79.

6. Frasch, CE. Production and Control of *Neisseria meningitidis* Vaccines, in Mizrahi A, ed. Advances in technological processes, vol. 13, Bacterial Vaccines, New York: Wiley-Liss, 1990, pp 123-145.

7. Zollinger WD, Boslego J, Moran E, Gracia J, Cruz C, Brandt B, Martinez M, Arthur J, Underwood P, Hankins W, Gilly J, the Chilean National Committee for Meningococcal Disease: Meningococcal serogroup B vaccine protection trial and follow-up studies in Chile. *NIPH Annals* 14:211, 1991.

8. Bjune G, Høiby EA, Grønnesby JK, Arnesen Ø, Fredriksen JH, Halstensen A, Holten E, Lindbak AK, Nøkleby H, Rosenqvist E, Solberg LK, Closs O, Eng J, Frøholm LO, Lystad A, Bakketeig LS, Hareide B. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. *Lancet* 338:1093-96, 1991.

9. Sierra VG, Campa HC, Garcia IL, et all. Efficacy evaluation of the Cuban vaccine VA-MENGOC-BC against disease caused by serogroup B *N. meningitidis*. In: Achtman M, Marchai C, Morelli G, Seiler A, Thiesen B, eds. Neisseria 1990. Berlin: Walter de Gruyter, 1991, pp 129-134.

10. De Moraes, JC, Perkins BA, Camargo MCC, Hidalgo NTR, Barbosa HA, Sacchi CT, Gral IML, Gattas VL, Vasconcelos HdG, Plikaytis, Wenger JD, Broome CV. Protective efficacy of a serogroup B meningococcal vaccine in São Paulo. *Lancet* 340:1074-78, 1992.

11. Frøholm LO, Berdal BP, Bøvre K et al. Meningococcal group B vaccine trial in Norway 1981-1982. *NIPH Ann* 6:133, 1983.

12. Nokleby H & Feiring B. The Norwegian meningococcal group B outer membrane vesicle vaccine: Side effects in phase II trials. *NIPH Ann* 14(2):85-102, 1991.

13. Frasch CE, Peppler MS, Cate TR, Zahvadnik JM. Immunogenicity and clinical evaluation of group B *Neisseria meningitidis* outer membrane protein vaccines. *Semin Infect Dis* 4:263, 1980.

14. Novo MV, Cruz RR, Molinert HT et al. La enfermedad meningocócica en Cuba: cronología de una epidemia. La Habana: Editorial Ciencias Médicas, 1991.

15. Schawartz B, Moore PS, Broome CV. Global epidemiology of meningococcal disease. *Clinical Microbiology Reviews* (2):118-124, 1989.

16. Children's Vaccine Initiative. Strategic Plan. CVI/93.2

17. Sistema Regional de Vacunas (SIREVA). Plan Maestro: Desarrollo de una vacuna perfeccionada anti-meningocócica, con énfasis en el serogrupo B. OPS, 1993.

Source: This article was prepared collaboratively by the Expanded Program on Immunization, Special Program on Maternal and Child Health and Population, the Division of Communicable Disease Prevention and Control, and the Division of Health and Development.

Fundamental principles of official statistics

The Economic Commission for Europe (ECE), at its forty-seventh session (1992), adopted decision C (47) on the fundamental principles of official statistics in the ECE region. This decision had been proposed unanimously to the ECE in 1991 by the Conference of European Statisticians. The Conference was of the opinion that decision C (47) was of universal significance, and requested that its contents be communicated to the United Nations Statistical Commission and to the other regional commissions of the United Nations.

In 1992 the Statistical Division of the United Nations Secretariat circulated a copy of the decision to all members of the Statistical Commission, the regional commissions and a number of other international organizations. Those countries and organizations which responded expressed support for similar principles at the global level.

The fundamental principles were considered by the Statistical Commission's Working Group on International Statistical Programs and Coordination at its sixteenth session (1993). The results of these deliberations, as well as the fundamental principles, were considered by the Statistical Commission at its special session (1994). The principles were accepted verbatim by the Commission and are reproduced below in their entirety.

1. Official statistics provide an indispensable element in the information system of a democratic society, serving the government, the economy and the public with data about the economic, demographic, social and environmental situation. To this end, official statistics that meet the test of practical utility are to be compiled and made available on an impartial basis by official statistical agencies to honor citizens' entitlement to public information.

2. To retain trust in official statistics, the statistical agencies need to decide according to strictly professional considerations, including scientific principles and professional ethics, on the methods and procedures for the collection, processing, storage and presentation of statistical data.

3. To facilitate a correct interpretation of the data, the statistical agencies are to present information according to scientific standards on the sources, methods and procedures of the statistics.

4. The statistical agencies are entitled to comment on erroneous interpretation and misuse of statistics.

5. Data for statistical purposes may be drawn from all types of sources, be they statistical surveys or administrative records. Statistical agencies are to choose the source with regard to quality, timeliness, costs and the burden on respondents.

6. Individual data collected by statistical agencies for statistical compilation, whether they refer to natural or legal persons, are to be strictly confidential and used exclusively for statistical purposes.

7. The laws, regulations and measures under which the statistical systems operate are to be made public.

8. Coordination among statistical agencies within countries is essential to achieve consistency and efficiency in the statistical system.

9. The use by statistical agencies in each country of international concepts, classifications and methods promotes the consistency and efficiency of statistical systems at all official levels.

10. Bilateral and multilateral cooperation in statistics contributes to the improvement of systems of official statistics in all countries.

Meetings, courses and seminaries

III Pan American Congress on Epidemiology, Córdoba, Argentina.

The Epidemiology Chapter of the Argentine Society for Hospital Administration and Medical Care, a branch of the Argentine Medical Association, and the School of Public Health of the School of Medical Sciences, National University of Córdoba, are promoting the III Pan American Congress on Epidemiology, to be held in the city of Córdoba, Argentina, 17-21 October 1994. The principal theme of the Congress is Epidemiology and the Organization and Evaluation of Health Services. Its main objective is to serve as a multidisciplinary and multi-institutional forum for the presentation, discussion, and dissemination of scientific papers and for sharing experiences in the field of epidemiology.
In addition, the aim is to strengthen epidemiological practice in the country, stimulate ideas with respect to the discipline, encourage the generation of knowledge about health, and promote the dissemination and utilization of this knowledge to define policies for reorienting national and international priorities in the organization and evaluation of health services. For additional information contact:

Escuela de Salud Pública
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The VII International Congress of the World Federation of Public Health ssociations

The VII International Congress of the World Federation of Public Health Associations will be held in Bali, Indonesia from 4-8 of December of 1994. The meeting is also sponsored by the World Health Organization, the Pan Americana Health Organization, the United Nations Childrens Fund, the United Nations Population Fund and the United Nations Development Programme.

The subject of the Congress will be Health, Economics and Development: Working Together for Change. For additional information contact:

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First Pan American Conference on Public Health Education

The Pan American Health Organization is sponsoring the I Pan American Conference on Public Health Education, joining together the efforts of the Latin American and Caribbean Association for Public Health Education (ALAESP) and the American Association of Schools of Public Health (ASPH). The Conference will be held in Rio de Janeiro, Brazil, 14-18 August 1994. This conference is part of several activities organized in commemoration of the fortieth anniversary of the Nacional School of Public Health of the Oswaldo Cruz Foundation in Rio. The Conference is based on the progress made through the PAHO/WHO project on "Development of the Theory and Practice of Public Health," and will be centered on the topic "Democracy and Equity: Rethinking Public Health." The contributions related to this initiative included the publication of the books "The Crisis of Public Health Reflections for the Debate" (1992) and " On the Theory and Practice of Public Health: One Debate, Several Perspectives" (1993), in addition to the reports on the national and subregional debates carried out in these subject fields in Latin America.
The agenda items include panel discussions on Contemporary Reforms in the Health Field: Proposals and Experiences, Current Approaches to the Theory and Practice of Public Health as well as presentations on specific thematic areas and group discussions on training in public health.

PAHO's Epidemiological Bulletin is published quarterly in English and Spanish.
Catalogued and indexed by the United States National Library of Medicine
Printed on acid-free paper.

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