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AEP Asociación Española de Pediatría
CAV Comité Asesor de Vacunas

Vacunas frente a meningococo B

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Epidemiología

- **Situaciones endémicas:**
  - Cepas con distribución heterogénea de los serotipos
  - 5-10% población (especialmente adolescentes) son portadores sanos
  - Dificultad para el desarrollo de una “vacuna universal”
    - En los últimos años se ha mantenido relativamente estable el porcentaje (30-40%) de las cepa B:4:P1.15 del complejo clonal ET5*
- **Situaciones epidémicas:**
  - Aparece un serotipo predominante. Ej: B:4:P1.7-2,4
  - “Vacuna a la carta”

*J. Vázquez. Enf Infecc Microbiol Clin. 2006

Desarrollo vacunas frente a meningococo B

- **Capsulares:**
  - Poco inmunógenas
  - Riesgo de autoinmunidad
- **No capsulares:**
  - Gran variabilidad antigénica
  - Protección cepas homólogas
  - Poca respuesta en lactantes
  - Inmunidad poco duradera: necesidad de dosis repetidas

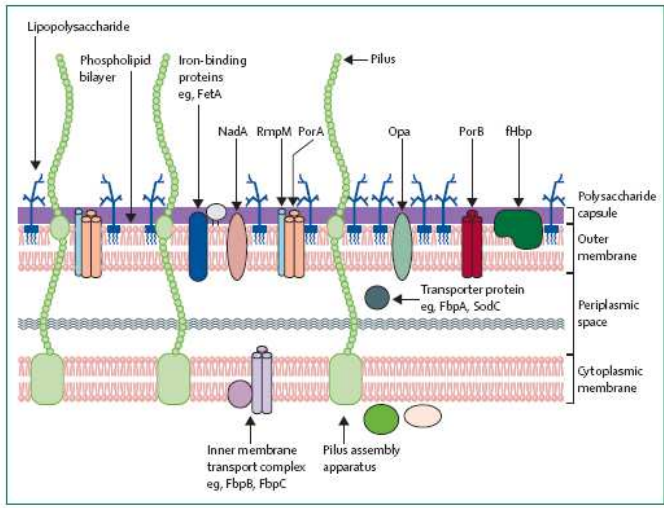


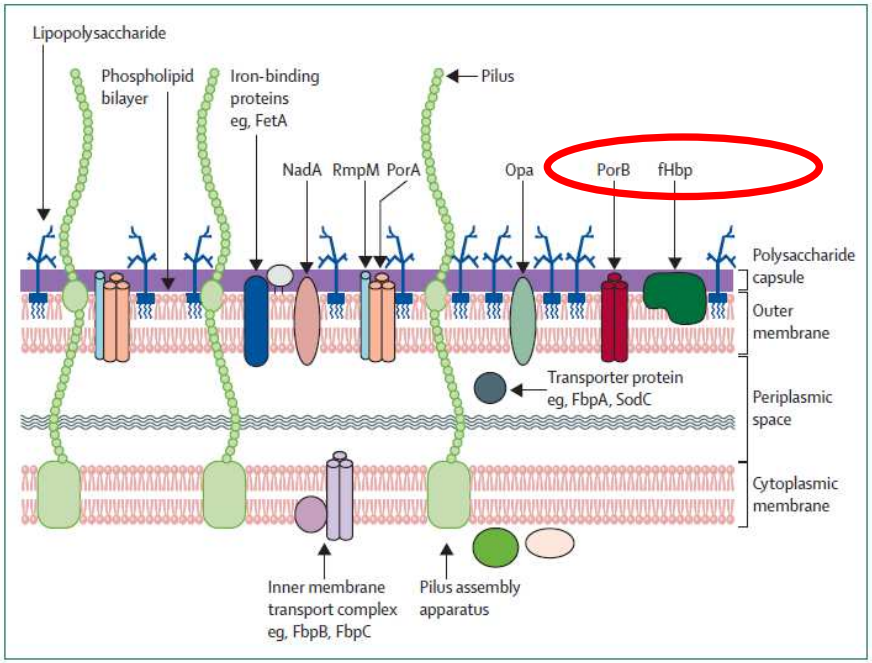
Figure 1: **Surface structures of *Neisseria meningitidis***
Serological classification of *N meningitidis* is based on capsule (serogroup), the outer membrane proteins PorB (serotype) and PorA (serosubtype), and lipopolysaccharide (immunotype). Other major outer membrane components include the new vaccine candidates fHbp and NadA.

Sadarangani M, Pollard AJ. Lancet Infect Dis.2010;10:112-24

Estrategias en el desarrollo de vacunas frente a meningococo B

Polisacárido capsular?	Proteína subcapsular aislada?	Múltiples componentes subcapsulares?
NO	Gran diversidad genómica y antigénica	Amplían la cobertura a múltiples cepas

N. meningiditis



Vacuna LP2086

VACUNA LP2086 (Pfizer)

- rLP2086= fHbp

- Es una lipoproteína nativa obtenida por técnicas recombinantes expresadas en *Escherichia coli* y después purificada

- Existen dos familias de LP2086: A y B. La vacuna contiene una mezcla bivalente de ambas

Ensayos clínicos Fase III en adolescentes.
Plan de presentación a la EMA en el año 2012

Componentes antigénicos de 4CMenB (Novartis)

Todos los antígenos incluidos en 4CMenB son importantes para la supervivencia, función o virulencia del meningococo

- **NadA: neisserial adhesin A**
  - Favorece la unión y penetración en las células epiteliales1-3
  - Posible papel en estado de portador
- **fHbp: factor H binding protein**
  - Inhibe la vía alternativa del complemento (in vitro)[4]
  - Induce respuesta de anticuerpos en humanos [5,6]
- **NHBA: neisserial heparin-binding antigen**
  - Presente practicamente en todas las cepas
  - Se une a la heparina, aumentando la resistencia de la bacteria[7-9]
- **NZ PorA 1.4: porin A**
  - Proteína de vesículas de membrana externa. Induce una potente respuesta de anticuerpos

1. Comanducci M, et al. *J Exp Med*. 2002;195:1445-1454; 2. Capecchi B, et al. *Mol Microbiol*. 2005;55:687-698; 3. Mazzon C, et al. *J Immunol*. 2007;179:3904-3916; 4. Veggi D, et al. Presented at IPNC. Banff, Canada. September 11-16, 2010; 5. Madico G, et al. *J Immunol.* 2006;177:501-510; 6. Schneider MC, et al. *J Immunol*. 2006;176:7566-7575; 7. Serruto D, et al. *Proc Natl Acad Sci U S A*. 2010;107:3770-3775; 8. Welsch JA, et al. *J Infect Dis*. 2003;188:1730-1740; 9. Plested, et al. *Clin Vaccine Immunol*. 2008;15:799-804.

Multicenter, Open-Label, Randomized Phase II Controlled Trial of an Investigational Recombinant Meningococcal Serogroup B Vaccine With and Without Outer Membrane Vesicles, Administered in Infancy

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Clinical Infectious Diseases 2010; 51(10):1127–1137

Background. In the absence of an efficacious broadly protective vaccine, serogroup B *Neisseria meningitidis* (MenB) is the leading cause of bacterial meningitis and septicemia in many industrialized countries. An investigational recombinant vaccine that contains 3 central proteins; Neisserial adhesin A (NadA), factor H binding protein (fHBP) and Neisserial heparin binding antigen (NHBA) has been developed. These antigens have been formulated with and without outer membrane vesicles (rMenB+OMV and rMenB, respectively) from the New Zealand epidemic strain (B:4:P1.7–2,4). In this trial, we assessed the immunogenicity of these formulations in infants, who are at greatest risk of contracting MenB disease.

Methods. A total of 147 infants from the United Kingdom were enrolled and randomly assigned to receive rMenB or rMenB+OMV at 2, 4, 6, and 12 months of age or a single dose at 12 months of age. Serum samples taken before and after vaccination were assayed in a standardized serum bactericidal antibody assay against 7 MenB strains. Local and systemic reactogenicity were recorded for 7 days after each vaccination. Analysis was according to protocol.

Results. After 3 doses, both vaccines were immunogenic against strains expressing homologous or related NadA and fHBP. rMenB+OMV demonstrated greater immunogenicity than did rMenB and was immunogenic against strains expressing homologous PorA. Both vaccines elicited anamnestic responses after the fourth dose. For both vaccines, responses were lower against strains expressing heterologous fHBP variants and after a single dose at 12 months.

Conclusions. The rMenB+OMV vaccine has the potential to protect infants from MenB disease, although the breadth of protection afforded to heterologous antigens requires additional investigation.

Immunogenicity and Tolerability of Recombinant Serogroup B Meningococcal Vaccine Administered With or Without Routine Infant Vaccinations According to Different Immunization Schedules

A Randomized Controlled Trial

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Context In the absence of an effective vaccine, serogroup B *Neisseria meningitidis* (MenB) remains a major cause of invasive disease in early childhood in developed countries.

Objective To determine the immunogenicity and reactogenicity of a multicomponent MenB vaccine (4CMenB) and routine infant vaccines when given either concomitantly or separately.

Design, Setting, and Participants Phase 2b, multicenter, open-label, parallel-group, randomized controlled study of 1885 infants enrolled at age 2 months from August 2008 to July 2010 in Europe.

Intervention Participants were randomized 2:2:1:1 to receive (1) 4CMenB at 2, 4, and 6 months with routine vaccines (7-valent pneumococcal and combined diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, *Haemophilus influenzae* type b vaccines); (2) 4CMenB at 2, 4, and 6 months and routine vaccines at 3, 5, and 7 months; (3) 4CMenB with routine vaccines at 2, 3, and 4 months; or (4) routine vaccines alone at 2, 3, and 4 months.

Main Outcome Measures Percentage of participants with human complement serum bactericidal activity (hSBA) titer of 1:5 or greater against 3 MenB strains specific for vaccine antigens (NZ98/254, 44/76-SL, and 5/99).

Results After three 4CMenB vaccinations, 99% or more of infants developed hSBA titers of 1:5 or greater against strains 44/76-SL and 5/99. For NZ98/254, this proportion was 79% (95% CI, 75.2%-82.4%) for vaccination at 2, 4, and 6 months with routine vaccines, 86.1% (95% CI, 82.9%-89.0%) for vaccination at 2, 4, and 6 months without routine vaccines, and 81.7% (95% CI, 76.6%-86.2%) for vaccination at 2, 3, and 4 months with routine vaccines. Responses to routine vaccines given with 4CMenB were noninferior to routine vaccines alone for all antigens, except for the responses to pertactin and serotype 6B pneumococcal polysaccharide. Fever was seen following 26% (158/602) to 41% (247/607) of 4CMenB doses when administered alone, compared with 23% (69/304) to 36% (109/306) after routine vaccines given alone and 51% (306/605) to 61% (380/624) after 4CMenB and routine vaccines administered together.

Conclusion A 4CMenB vaccine is immunogenic against reference strains when administered with routine vaccines at 2, 4, and 6 or at 2, 3, and 4 months of age, producing minimal interference with the response to routine infant vaccinations.

Trial Registration clinicaltrials.gov Identifier: NCT00721396

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MENINGOCOCCAL DISEASE occurs with an incidence of 0.2 to 14 per 100 000 population in industrialized countries.[1] Effective vaccines based on capsular polysaccharides for meningococcal serogroups A, C, W-135, and Y are available,[2] but sero-

Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study

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Summary

Background Effective glycoconjugate vaccines against *Neisseria meningitidis* serogroups A, C, W-135, and Y have been developed, but serogroup B remains a major cause of severe invasive disease in infants and adolescents worldwide. We assessed immunogenicity and tolerability of a four-component vaccine (4CMenB) in adolescents.

Methods We did a randomised, observer-blind, placebo-controlled, study at 12 sites in Santiago and Valparaíso, Chile. Adolescents aged 11–17 years received one, two, or three doses of 4CMenB at 1 month, 2 month, or 6 month intervals. Immunogenicity was assessed as serum bactericidal activity using human complement (hSBA) against three reference strains for individual vaccine antigens, and assessed by ELISA against the fourth strain. Local and systemic reactions were recorded 7 days after each vaccination, and adverse events were monitored throughout the study. Participants were initially randomised to five groups (3:3:3:3:1) during the primary phase to receive either one dose, two doses 1 or 2 months apart, or three doses of 4CMenB, or three doses of placebo, with an additional three groups generated for the booster phase. All subjects received at least one dose of 4CMenB. Geometric mean titres, proportions of participants with serum bactericidal antibody titres of 4 or more, and Clopper-Pearson 95% CIs were calculated. The study is registered with ClinicalTrials.gov, number NCT00661713.

Findings Overall, 1631 adolescents (mean age 13·8 [SD 1·9] years) received at least one dose of 4CMenB. After two or three doses, 99–100% of recipients had hSBA titres of 4 or more against test strains, compared with 92–97% after one dose ($p<0·0145$) and 29–50% after placebo. At 6 months 91–100% of participants still had titres of 4 or more for each strain after two or three doses, but only 73–76% after one dose; seroresponse rates reached 99–100% for each strain after second or third doses at 6 months. Local and systemic reaction rates were similar after each 4CMenB injection and did not increase with subsequent doses, but remained higher than placebo. No vaccine-related serious adverse events were reported and no significant safety signals were identified.

Interpretation On the basis of immunogenicity responses this study provides evidence for an adolescent 4CMenB vaccine schedule of two doses, 1–6 months apart, to provide protection against meningococcal B infection. The extent of this protection against meningococcus B variants circulating worldwide will be determined by national surveys.

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Recombinant protein meningococcal serogroup B vaccine combined with outer membrane vesicles

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8. Expert opinion

Evaluations of the Novartis investigational MenB vaccines have led to the development of a final formulation of Bexsero. This vaccine has been shown to induce immune responses in preclinical studies and clinical trials reported across all age groups. Latest data from infant trials showed that the large majority of infants displayed a robust immune response against MenB reference strains and that the vaccine has acceptably low reactogenicity rates when given in conjunction with other infant immunisations. These data suggest that Bexsero offers several distinct advantages over existing OMV vaccines. It offers broader coverage of MenB isolates and has multiple antigens, each with different functional properties, which enable control of meningococcal infection through distinct mechanisms that reduce the chances of bacterial mutation and survival. Importantly, it has elicited good immune responses and anamnestic responses have been demonstrated following booster doses. The vaccine is well tolerated in all age groups and may be co-administered with other routine vaccines as part of a flexible vaccination schedule. Ongoing work will produce further supporting evidence and address the persistent antibody response in infants and adolescents, effect on acquisition of carriage in young adults and the ability to induce herd immunity.

Results from clinical trials are based on a small number of MenB target strains, which have demonstrated that infant's responses are less cross-reactive than those of toddlers following a booster dose and in turn older age groups. Further work is required to fully determine that breadth of cross-reactivity at the different age groups for each of the vaccine antigens. Equally, persistence data following both infant and later schedules, when available, will enable predictions of the likely length of protection afforded. Despite overall coverage of this vaccine being reported in a collection of invasive strains examined by MATS, more data are needed to show the protection afforded by Bexsero against each country's meningococcal strain population.

In conclusion, comprehensive clinical trial data from more than 7500 subjects from a range of age groups, including infants has characterised the safety and immunogenicity profile of Bexsero. Initial genotypic estimates of the potential coverage of the vaccine look promising, and MATS data to provide more detailed phenotypic coverage estimates are eagerly anticipated. Bexsero has been submitted to the European Medicines Agency for marketing authorisation in December 2010 and additional Phase III trial results from ongoing studies are expected in autumn 2011 [105]. Bexsero could be the first vaccine to provide broad-protective immunity against diverse MenB populations responsible for invasive disease.

4CMenB: Proposed Indications

Proposed indications	Population	Age	Dose series	Interval	Booster recommended
	Infants	2 to 5 months	3	1 to 2 months	At 12 to 23 months
	Unvaccinated infants	6 to 11 months	2	2 months	At 12 to 23 months; ≥2 months from primary series
	Unvaccinated toddlers and children	12 months to 10 years	2	≥2 months	
	Adolescents and adults	11 years and older*	2	1 to 2 months	

*The safety and immunogenicity of 4CMenB in individuals older than 50 years have not been studied.

Resumen

- Meningococo B es una bacteria con **gran variabilidad genética y antigénica**

- **Vacuna 4CMenB (Novartis)**
  - Incluye 4 proteínas importantes para la supervivencia y/o virulencia del meningococo: **fHbp, NadA, NHBA, y PorA**
  - En los estudios clínicos en niños a partir de 2 meses de edad se ha comprobado una **buena inmunogenicidad y aceptable tolerabilidad**
  - Puede ofrecer protección frente al 78% de las cepas de meningococo B circulantes en Europa
  - Presentada a la EMA en diciembre 2010, pendiente autorización

- **La vacuna LP2086 (Pfizer)**
  - Incluye las dos familias **(A y B) de la LP2086** = fHbp
  - Ensayos clínicos fase III en adolescentes, fase I en lactantes
  - Plan de presentación a la EMA en el año 2012