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COMMENTARY

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Cross-protection induced by VA-MENGOC-BC® vaccine

Rolando Felipe Ochoa-Azze

Department of Immunology, Institute of Basic and Preclinical Sciences, University of Medical Sciences, Senior Researcher at the Finlay Institute of Vaccines, Havana, Cuba

ABSTRACT

I would like to comment on the article "*Commentary: Impact of meningococcal group B OMV vaccines, beyond their brief*", DOI: 10.1080/21645515.2017.1381810. The author states that meningococcal group B OMVs vaccines –such as VA-MENGOC-BC®– may induce moderate protection against *Neisseria gonorrhoeae*. I agree. However, the author states that "*there was no evidence of effectiveness in the younger children*." The effectiveness of VA-MENGOC-BC® in heterologous contexts has been higher than 80% in individuals older than 4 years old, but the effectiveness in younger children should not be undervalued; it has usually been higher than 60%, and results markedly higher when evaluated based on mortality rates. There is strong evidence that VA-MENGOC-BC® may induce cross-protection against heterologous *N. meningitidis* strains and *N. gonorrhoeae*.

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Introduction

Outer membrane vesicle (OMV) vaccines have been used to control serogroup B outbreaks. MenBvac (Norwegian Institute of Public Health, NIPH) was used to control an epidemic in Normandy, France, caused by the B:15:P1.7,16 strain. The MeNZB vaccine (Chiron and NIPH) controlled an epidemic in New Zealand produced by the B:4:P1.7–2,4 strain, and VA-MENGOC-BC® (Finlay Institute) was successfully used to control a huge epidemic of meningococcal disease in Cuba, caused by the B4:P1.19,15 hypervirulent strain.[1-5] Nevertheless, the effectiveness of these vaccines in heterologous contexts has been questioned.

OMVs from *Neisseria meningitidis* contain a cocktail of immunogenic antigens, including lipo-oligosaccharide and several different outer-membrane proteins, out of which the porin protein, PorA, has been considered the principle antigenic source of bactericidal antibodies. However, PorA is highly variable across *Neisseria meningitidis* strains.[1,2] For that reason, new approaches have been evaluated for new vaccines, including those based on reverse vaccinology that have identified common proteins to different strains, and generation of recombinant proteins.[6-11]

However, we have to take into account the minor OMV components that could potentially generate cross-reactivity inducing broader protection. These particles possess self-adjuvancity and they induce not only a strong bactericidal response by activating the classical pathway of the complement system, but also by facilitating the opsonization mechanism of phagocytosis, stimulating neutrophils and other phagocytic cells, interfering with the bacterial iron metabolism, inducing mucosal immunity, and modifying the carrier state, among other immune mechanisms.[4,12]

Nevertheless, the immunogenicity evaluation of meningococcal vaccines has been limited to serum bactericidal assays, the gold standard, underestimating the broad protection induced by meningococcal vaccines.[4,12,13]

VA-MENGOC-BC® is composed of OMVs from the B4:P1.19,15:L3,7,9 strain and capsular polysaccharide of meningococcus C.[3] The OMVs have been obtained from a hypervirulent strain, which was chosen precisely considering the expression of minor components that may be present in heterologous strains.

The correct choice of the vaccine strain and the production know-how allow the OMVs of this vaccine to have more than one hundred proteins, including 31 predicted ones. It includes: PorA, PorB, Opa, Opc, Tbp, NspA, NadA, FbpA, FetA, HrpA, PilQ, fHbp, NMB0088, NMB1796, NMB0928, ATP-synthetases, bacterioferritins, heat shock proteins and ribosomal proteins, among other components.[14,15]

On the other hand, a study published in 2014 by researchers of the University of Southampton and GlaxoSmithKline Pharmaceutical, showed that VA-MENGOC-BC® induces bactericidal antibodies with broad cross-reactivity. They also identified novel antigens such as exopolyphosphatase, γ-glutamyltranspeptidase and a putative cell-binding factor protein.[16]

The author of "*Commentary: Impact of meningococcal group B OMV vaccines, beyond their brief*" (DOI: 10.1080/21645515.2017.1381810) states that meningococcal group B OMV vaccines –like VA-MENGOC-BC– may induce moderate

CONTACT Rolando Felipe Ochoa-Azze, MD, PhD rochoa@infomed.sld.cu 27 Avenue No. 19805, Havana, Cuba.

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protection against *N. gonorrhoeae*.[17] I agree with this point of view. However, the author states that the heterologous effect against diverse strains of meningococcus is limited to older children and adults.

In this Letter to the Editor, the effectiveness of VA-MENGOC-BC® in reducing meningococcal disease caused by homologous or heterologous serogroup B strains was analyzed by age group.

Methods

Scientific papers on VA-MENGOC-BC® composition and the vaccine efficacy in the pre-licensure phase III clinical trial were reviewed. This was the Cuban study designed to evaluate whether the VA-MENGOC-BC® vaccine produced the expected result under ideal circumstances, that is, in a randomized, double-blind, placebo-controlled trial based on a clinical disease endpoint.

Results of the published post-marketing observational studies on VA-MENGOC-BC® application in Cuba, Brazil, Uruguay and Colombia were analyzed. The effectiveness against meningococcal disease caused by the vaccine strain (homologous) and meningococcal B strains different than the one used in the vaccine (heterologous) was evaluated in several age groups.

Vaccine effectiveness was defined in the post-marketing observational studies as the degree of protection attributable to the vaccine when administered under field conditions.

Furthermore, the impact of vaccination on the meningococcal disease burden in Cuba and Uruguay, as well as the phenotypic and genetic structure of *Neisseria meningitidis* populations in Cuban patients and carriers, during the pre- and post-vaccination periods were analyzed.

Results and discussion

VA-MENGOC-BC® OMVs are obtained from a hypervirulent strain, which caused a large epidemic outbreak in Cuba in the 80's of the past century. Conceptually, it could be considered a "tailor-made" vaccine, since the B:4:P1.19,15 strain caused most of the cases. However, since the beginning of the vaccine development, the expression of cross-reactive antigens that would induce protection not only against homologous strains, but also against heterologous ones was considered. These requirements were taken into account for the selection of the vaccine strain and the development of the production know-how.[3,18]

In 1987, a Phase III efficacy trial of VA-MENGOC-BC® was conducted. It was a controlled, double-blind, randomized trial, with the participation of 106,251 boarding school students, aged 10–16 years, using a two-dose schedule with a 6–8 week interval. The trial was carried out in the 7 Cuban provinces with the highest incidence of the disease and lasted 16 months. The estimated efficacy was 83%. A similar result was achieved in a cohort study performed in children under 4 years old (886,148 children; 85% vaccinated).[3,4,18]

The strategy of the Cuban Ministry of Public Health (MINSAP) to combat the meningococcal epidemic was carried out in two stages. The first was a nationwide mass vaccination campaign from 1989 to 1990, targeting the highest-risk population aged 3 months to 24 years and involving over 3 million people, which achieved a general coverage of 95%. The main objective of this stage was to stop the increase in disease incidence. During the second stage, begun in 1991, which continues to date, VA-MENGOC-BC® was included in the Expanded Program of Immunization, using a two-dose schedule: the first dose at 3 months and the second, at 5 months of age. The objective of this stage was to protect all children born after the mass vaccination campaign, in order to prevent new epidemic outbreaks among susceptible population accumulating over time. In addition, VA-MENGOC-BC® has been routinely used in other risk groups.

This strategy has proven correct. The morbidity rates dropped from 14.4 × 100,000 inhabitants during the epidemic period to 0.1 × 100,000. The effectiveness of the vaccine has ranged from 80% to 100% in infants, children, adolescents and adults. The mean effectiveness in infants (<one year old) was 84% between 1997 and 2008, and reached 93% in preschool children. In recent years, the incidence rates of meningococcal disease have been lower than 0.1 × 100,000 inhabitants.[3,4,18,19]

VA-MENGOC-BC® has been widely used to control serogroup B outbreaks in various countries. Of course, epidemiological situations in other countries differ from the Cuban one, in many cases there is wide circulation of heterologous strains.

In Sao Paulo, Brazil, Cassio de Moraes and coworkers performed an ambispective case-control study (112 cases; 409 controls) at the beginning of the 90's of the past century. It was designed to estimate VA-MENGOC-BC® effectiveness against meningococcal disease in children between 3 months and 6 years of age.[20] The reported effectiveness against serogroup B of this study was 73% in children above 4 years old, and it was 33% in children under 4 years of age, however for the prospective branch of the study, the estimated effectiveness was 55%. About 60% of cases were produced by heterologous strains, for that reason they concluded: *"The finding suggests that the vaccine can provide protection against some serogroup B meningococcal strains other than the vaccine type-strain"*.

On the other hand, other trials performed in Brazil during those years showed higher effectiveness. In the State of Santa Catarina, the effectiveness against serogroup B was evaluated in a retrospective cohort study (400,482 vaccinated children; 89,610 unvaccinated). It was 66% in children younger than 4 years old, and 88% in children above 4 years old.[21] In the City of Rio de Janeiro, a retrospective case-control study (275 cases; 279 controls) was carried out in children between 6 months and 9 years of age. The calculated effectiveness was 64% in children younger than 4 years old, and 82% in children above 4 years of age.[22]

Moreover, the Health Ministry of Brazil assessed the impact of vaccination with VA-MENGOC-BC® in six Brazilian states, including those that we have referred to. The effectiveness reported against serogroup B was 72% in children between 6 and 83 months of age.[23]

Regarding the lower protective effectiveness for children younger than 4 years old, reported in the study published by Moraes and coworkers in which only laboratory-confirmed cases were analyzed, it could be partially due to a selective effect

of this procedure. The exclusion from the study of those cases not confirmed by laboratory analysis decreases the effectiveness of the vaccine because severe cases occurred in non-vaccinated children, who died before reaching the hospital. Vaccinated children who contracted the disease presented an attenuated clinical situation, allowing them to reach the hospital, where laboratory diagnosis could be performed.

On the other hand, the lower effectiveness for this study, as compared with other Brazilian studies, was also apparently related to the retrospective and prospective enrollment of cases to increase the sample size, which probably caused biased results. For the retrospective part of the study, estimated vaccine coverage was only 5%, but the actual vaccination coverage of the population was 12%. Data for the controls underestimated vaccine coverage. For the prospective part, the estimated and actual coverage were 93% and 92% respectively, and effectiveness increased to 55%.[20,23]

The effectiveness reported in Brazil is significant. The great diversity of meningococcal serosubtypes reported, supports cross protection induced by VA- MENGOC-BC®.

The higher effectiveness against heterologous strains in older age groups could be related to the maturation of the immune system, but it is also necessary to consider the increasing exposure to *Neisseria meningitidis*, due to the carrier state or the close contact with carriers; either at home, school or work. In this situation, the booster effect induced by common components of outer membrane vesicles increases. However, the levels of protection achieved in children younger than 4 years of age should not be undervalued.

VA-MENGOC-BC® was also used in Colombia during the epidemic in Itaguí, Antioquia, in children between 3 months and 4 years of age. Effectiveness was assessed in a cohort study (16,762 children; 92% vaccinated), and it was higher than 98%, greater than the effectiveness determined by Cuban and Brazilian researchers.[24]

In Uruguay, the vaccine was also used to control an outbreak in individuals between 4 and 19 years old. The morbidity and mortality rates dropped dramatically after vaccination. In the department of Canelones 443,053 individuals were vaccinated (81% vaccination coverage), and morbidity decreased from 7.4 × 100,000 inhabitants in the epidemic period, to 0 in the post-vaccination one. Although the vaccine serosubtype predominated in the most severe cases of meningococcal disease, about 50% of cases were caused by heterologous strains.[25]

In the department of Montevideo, 1,344,839 individuals were vaccinated (73% vaccination coverage), and the morbidity rate declined slightly: from 4.6 × 100,000 inhabitants in the epidemic period, to 3.4 × 100,000 inhabitants after vaccination. Heterologous strains were isolated in most patients with meningococcal disease (83.87%) during the epidemic period.[25]

The effectiveness was 88% in Montevideo and 100% in Canelones. Since most of the strains isolated in Montevideo were heterologous, we must consider that vaccine protection is not strictly limited to the vaccine strain.

A summary of these observational studies is displayed in Table 1.

Additional analyses in heterologous-strain contexts were carried out in children younger than 2 years old, and children between 2 and 4 years old, when data were available.

In the city of Rio de Janeiro, the effectiveness against confirmed serogroup B strains was 69% in children between 2 and 4 years of age and 47% in children younger than 2 years old. It is noteworthy that the effectiveness defined by any criteria was higher in children less than 4 years. The protection against severe clinical manifestations of meningococcal disease was 67% in children less than 2 years of age.[22]

In the state of Santa Catarina, the effectiveness increased when the analysis was restricted to cases that could be classified as *Neisseria meningitidis* serogroup B: 66% in children between 3 months and 4 years old and 88% in those over 4 years. However, data were not available for children between 2 and 4 years old, and younger than 2 years old. On the other hand, if effectiveness was evaluated based on mortality rates, it rose to 76% in children under 4 years of age.[21]

In these Brazilian studies, the lowest effectiveness was found in children less than 2 years old, however, the effectiveness in these children should not be undervalued. On the other hand, it markedly increased when the evaluation was based on severe clinical scenarios (Table 2).

It should be taken into account that a two-dose immunization schedule with a 6 to 8 week interval was used, and other studies have demonstrated that three doses of VA-MENGOC-BC® and other OMV vaccines, increases immunogenicity against heterologous strains.[26,27]

The protection against heterologous serogroup B strains could be due to cross-reactive antigens that have been identified on the OMVs of this vaccine. These include not only well-

Table 1. Effectiveness of VA-MENGOC-BC® against serogroup B meningococcal disease.

Location (Date)	Age group	Effectiveness by age group	
		<4 years old	>4 years old
7 Provinces/Cuba (1987–1989)	10–16 years	—	83%
14 Provinces/Cuba (1989–1994)	3 months-4 years	81%	—
Cuba (1997–2008)	<1 year	84%	—
12 Provinces/Cuba (1988–1990)	3 months-4 years	93%	—
Santa Catarina/Brazil (1990–1992)	3 months-7 years	66%	88%
Rio de Janeiro/Brazil (1990–1992)	6 months-9 years	64%	82%
Sao Paulo/Brazil (1990–1991)	3 months-6 years	33% (55%*)	73%
Antioquia/Colombia (1991–1994)	3 months-4 years	98%	—
Canelones/Uruguay (2002–2003)	4–19 years	—	100%
Montevideo/Uruguay (2002–2003)	4–19 years	—	88%

*Effectiveness in the prospective branch of the study.

Table 2. Effectiveness of VA-MENGOC-BC® in analytical observational studies carried out in Rio de Janeiro and Santa Catarina, Brazil.

	Rio de Janeiro (1990–1992)		Santa Catarina (1990–1992)	
Years	B	All	B	All
<2	47%	53% (67%*)	n.a.	55%
2–4	69%	77%	n.a.	62%
<4	64%	64%	66%	59% (76%**)
>4	82%	80%	88%	78%

B = Effectiveness against serogroup B meningococcal disease (*Neisseria meningitidis* isolated from a culture of cerebrospinal fluid (CSF) or blood, and meningococcal antigens demonstrated in CSF or serum by counter-immunoelectrophoresis or latex agglutination).
All = Effectiveness against meningococcal disease (*Neisseria meningitidis* serogroup B was not studied. Cases were defined by clinical criteria and laboratory tests).
n.a. = data not available.
*Effectiveness against severe clinical manifestations of meningococcal disease.
**Effectiveness based on mortality rates.

studied antigens, but also novel antigens that could be useful for developing new generation meningococcal vaccines.[14–16]

Phenotypic characterization of strains isolated in carriers during epidemic and post-epidemic stages complements the studies aimed at assessing the role of vaccination as an intervention measure. In this regard, Martínez and colleagues characterized *Neisseria meningitidis* strains for 20 years. They showed that during the epidemic stage in Cuba, serogroup B (67.62%), serotype 4 (70.48%) and subtype P1.19,15 (61.91%) predominated and during the post-vaccination period, non-serogroupable (NG) (79.65%) non-serotypable (NT) (70.8%) and non-serosubtypable (NST) (34.36%) prevailed. Thus, the predominant phenotype during the epidemic was: B:4:P1.19,15:L3,7,9; favorably changed in the post-vaccination period to the phenotype NG:NT:P1.NST:L3,7,9.[28]

Climent and colleagues studied the impact of vaccination on the distribution of strains in patients and carriers in the pre and post-vaccination periods. Strains from 12 clonal complexes were isolated. The main strain that caused the outbreak in Cuba belonged to the ST-32 complex (58.6% of the isolates). It was demonstrated that VA-MENGOC-BC® was effective against the ST-32, ST-41/44, ST-8 and ST-11 complexes, among others. Likewise, the carrier state was modified with decrease of the hypervirulent lineages. The ST-53 complex, common in asymptomatic carriers, became predominant after vaccination.[29,30]

The protection induced by VA-MENGOC-BC® is not strictly limited to the vaccine strain. On the other hand, Dr Helen Petousis states that there is strong evidence that OMV vaccines against *Neisseria meningitidis* may induce moderate protection against *Neisseria gonorrhoeae*.[17] Data clearly show a decline in the incidence of gonorrhoea in Cuba following vaccination with VA-MENGOC-BC® especially after the massive catch-up immunization campaign.[31,32] These results prove that this vaccine induces cross-reactive protection against pathogenic *Neisseria* species.

Provision of booster doses of VA-MENGOC-BC® at an age prior to sexual debut, after priming during infancy could contribute to protection against gonorrhoea, as well as improving population immunity against *Neisseria meningitidis*.

Disclosure of potential conflicts of interest

The author has been scientific advisor of the Finlay Institute of Vaccines, but he did not receive any honorarium for this paper were disclosed.

ORCID

Rolando Felipe Ochoa-Azze http://orcid.org/0000-0002-8008-2944

References

1. Oviedo-Orta E, Ahmed S, Rappuoli R, Black S. Prevention and control of meningococcal outbreaks: The emerging role of serogroup B meningococcal vaccines. Vaccine 2015;33(31):3628–35. doi:10.1016/j.vaccine.2015.06.046. PMID:26093201.
2. Bianchi A, Fantoni S, Prugnola A. Meningococcal B vaccine and the vision of a meningitis free world. J Prev Med Hyg. 2015;56(3):E140–3. PMID:26788735.
3. Sotolongo F, Campa C, Casanueva V, Fajardo E, Cuevas, I, González N. Cuban meningococcal BC vaccine: experiences & contributions from 20 years of application. MEDICC Rev. 2007;9(1):16–22. PMID:21487356.
4. Ochoa RF, Sierra G. Vacunas contra la enfermedad meningocócica. In: Ochoa RF, Menéndez J, editor(s), Prevención de la enfermedad meningocócica. 1st ed. La Habana, Cuba: Finlay Ediciones; 2010. pp. 67–84. (Spanish)..
5. Galloway Y, Stehr-Green P, McNicholas A, O`Hallahan J. Use of an observational cohort study to estimate the effectiveness of the New Zealand group B meningococcal vaccines in children aged under 5 years. Int J Epidemiol. 2009;38(2):413–8. doi:10.1093/ije/dyn228. PMID:18988650.
6. McNeil LK, Zagursky RJ, Lin SL, Murphy E, Zlotnick GW, Hoiseth SK, Jansen KU, Anderson A. Role of factor H binding protein in *Neisseria meningitidis* virulence and its potential as a vaccine candidate to broadly protect against meningococcal disease. Microbiol Mol Biol Rev. 2013;77(2):234–52. doi:10.1128/MMBR.00056-12. PMID:23699256.
7. Santolaya ME, ORyan ML, Valenzuela MT, Prado V, Vergara R, Muñoz A, Toneatto D, Graña G, Wang H, Clemens R, Dull PM. 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. Lancet 2012;379(9816):617–24. doi:10.1016/S0140-6736(11)61713-3..
8. Gossger N, Snape MD, Yu LM, Finn A, Bona G, Esposito S, Principi N, Diez-Domingo J, Sokal E, Becker B, et al. 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. JAMA. 2012;307(6):573–82. doi:10.1001/jama.2012.85. PMID:22318278.
9. Donald RGK, Hawkins JC, Hao L, Liberator P, Jones TR, Harris SL, Pérez JL, Eiden JJ, Jansen KU, Anderson AS. Meningococcal serogroup B vaccines: Estimating breadth of coverage. Hum Vaccin Immunother. 2017;13(2):1–11. doi:10.1080/21645515.2017.1264750..
10. Basta NE, Mahmoud AAF, Wolfson J, Ploss A, Heller BL, Hanna S, Johnsen P, Izzo R, Grenfell BT, Findlow J, et al. Immunogenicity of a meningococcal B vaccine during a university outbreak. N Engl J Med. 2016;375(3):220–8. doi:10.1056/NEJMoa1514866. PMID:27468058.

11. Read RC, Dull P, Bai X, Nolan K, Findlow J, Bazar R, Kleinschmidt A, McCarthy M, Wang H, Toneatto D, Borrow R. A phase III observer-blind randomized, controlled study to evaluate the immune response and the correlation with nasopharyngeal carriage after immunization of university students with a quadrivalent meningococcal ACWY glycoconjugate or serogroup B meningococcal vaccine. Vaccine 2017;35(3):427–34. doi:10.1016/j.vaccine.2016.11.071. PMID:27912986.
12. Pérez O, Lastre M, Lapinet J, Bracho G, Díaz M, Zayas C, Taboada C, Sierra G. Immune response induction and new effector mechanisms possibly involved in protection conferred by the Cuban Anti-Meningococcal BC vaccine. Infect Immun. 2001;69(7):4502–8. doi:10.1128/IAI.69.7.4502-4508.2001. PMID:11401992.
13. Vermont C, van den Dobbelsteen G. *Neisseria meningitidis* serogroup B: laboratory correlates of protection. FEMS Immunol Med Microbiol. 2002;34(2):89–96. doi:10.1111/j.1574-695X.2002.tb00608.x. PMID:12381458.
14. Uli L, Castellanos-Serra L, Betancourt L, Domínguez F, Barberá R, Sotolongo F, Guillén G, Pajón R. Outer membrane vesicles of the VA-MENGOC-BC® vaccine against serogroup B of *Neisseria meningitidis*: Analysis of protein components by two-dimensional gel electrophoresis and mass spectrometry. Proteomics. 2006;6(11):3389–99. doi:10.1002/pmic.200500502. PMID:16673438.
15. Gil J, Betancourt LH, Sardiñas G, Yero D, Niebla O, Delgado M, García D, Pajón R, Sánchez A, González LJ, et al. Proteomic study via a non-gel based approach of meningococcal outer membrane vesicle vaccine obtained from strain CU385: A road map for discovering new antigens. Hum Vaccin. 2009;5(5):347–56. doi:10.4161/hv.5.5.7367. PMID:19377283.
16. Williams JN, Weynants V, Poolman JT, Heckels JE, Christodoulides M. Immuno-proteomic analysis of human immune responses to experimental *Neisseria meningitidis* outer membrane vesicle vaccines identifies potential cross-reactive antigens. Vaccine. 2014;32(11):1280–6. doi:10.1016/j.vaccine.2013.12.070. PMID:24486354.
17. Petousis-Harris H. Commentary: Impact of meningococcal group B OMV vaccines, beyond their brief. Hum Vaccin Immunother. 2017 Oct;19:1–6 doi:10.1080/21645515.2017.1381810..
18. Sierra GV, Campa HC, Valcárcel NM, García IL, Izquierdo PL, Sotolongo PF, Casanueva GV, Rico CO, Rodríguez CR, Terry MH. Vaccine against group B *Neisseria meningitidis*: protection trial and mass vaccination results in Cuba. NIPH Ann. 1991;14(2):195–210. PMID:1812432.
19. Pérez A, Dickinson F, Rodríguez M. Efectividad de la vacuna antimeningocócica VA-MENGOC-BC® en el primer año de vida, Cuba, 1997–2008. Rev Cubana Med Trop. 2011;63(2):155–60. (Spanish). PMID:23437524.
20. De Moraes JC, Perkins BA, Camargo MCC, Hidalgo NTR, Barbosa HA, Sacchi CT, Gral IML, Gattas VL, Vasconcelos HG, Plikaytis BD, et al. Protective effectiveness of a serogroup B meningococcal vaccine in Sao Paulo, Brazil. Lancet. 1992;340(8827):1074–8. doi:10.1016/0140-6736(92)93086-3. PMID:1357461.
21. Costa E, Martins HJ, Klein CH. Avaliação da proteção conferida pela vacina antimeningocócica BC no Estado de Santa Catarina, Brazil, 1990/92. Rev Saúde Pública. 1996;30(5):460–70. (Portuguese). doi:10.1590/S0034-89101996000500009..
22. Noronha CP, Struchiner CJ, Halloran ME. Assessment of the direct effectiveness of BC meningococcal vaccine in Rio de Janeiro, Brazil: A case-control Study. Int J Epidemiol. 1995;24(5):1050–7. doi:10.1093/ije/24.5.1050. PMID:8557439.
23. Costa EA. On the Controversy about the effectiveness of the antimeningococcal B Vaccine: methodological pitfalls. Cad Saúde Pública 1995;11(2):332–5. doi:10.1590/S0102-311X1995000200018..
24. Galeano LA, Echeverry ML. Efectividad de una vacuna antimeningocócica en una cohorte de Itaguí, Colombia, 1995. Boletín Epidemiológico de Antioquia. 1995;20(2):110–8. (Spanish)..
25. Pírez MC, Picón T, Galazka J, Rubio I, Montano A, Ferrari AM. Control de un brote epidémico de enfermedad meningocócica por *Neisseria meningitidis* serogrupo B. Rev Méd Urug. 2004;20(2):92–101. (Spanish)..
26. Morley S, Cole M, Ison C, Camaraza MA, Sotolongo F, Anwar N, Cuevas I, Carbonero M, Campa C, Sierra G, Levin M. Immunogenicity of a serogroup B meningococcal vaccine against multiple *Neisseria meningitidis* strains in infants. Pediatr Infect Dis J. 2001;20(11):1054–61. doi:10.1097/00006454-200111000-00010. PMID:11734711.
27. Boutriau D, Poolman J, Borrow R, Findlow J, Diez-Domingo J, Puig-Barbera J, Baldó JM, Planelles V, Jubert A, Colomer J, et al. Immunogenicity and safety of three doses of a bivalent (B:4:P1.19,15 and B:4:P1.7-2,4) meningococcal outer membrane vesicle vaccine in healthy adolescents. Clin Vaccine Immunol. 2007;14(1):65–73. doi:10.1128/CVI.00230-06. PMID:17065257.
28. Martínez I, Sierra G, Núñez N, Izquierdo L, Mirabal M. Caracterización de cepas de *Neisseria meningitidis* aisladas de portadores en Cuba durante 20 años. Rev Cubana Med Trop. 2006;58(2):124–33. (Spanish). PMID:23427430.
29. Climent Y, Yero D, Martínez I, Martín A, Jolley KA, Sotolongo F, Maiden MV, Urwin R, Pajón R. Clonal distribution of disease-associated and healthy carrier isolates of *Neisseria meningitidis* between 1983 and 2005 in Cuba. J Clin Microbiol. 2010;48(3):802–10. doi:10.1128/JCM.01653-09. PMID:20042619.
30. Climent Y, Urwin R, Yero D, Martínez I, Martín A, Sotolongo F, Maiden MC, Pajón R. The genetic structure of *Neisseria meningitidis* populations in Cuba before and after the introduction of a serogroup BC vaccine. Infect Genet Evol. 2010;10(4):546–54. doi:10.1016/j.meegid.2010.02.002. PMID:20156598.
31. Perez O, del Campo J, Cuello M, González E, Núñez N, Cabrera O, Llanes R, Acevedo R, Zayas C, Balboa J, et al. Mucosal approaches in *Neisseria* Vaccinology. VacciMonitor 2009;18(2):53–5..
32. Cuello M, Cabrera O, Acevedo R, Núñez N, del Campo J, Lastre M, Zayas C, González E, Balboa J, Romeu B, et al. Nasal immunization with AFCo1 induces immune response to *N. gonorrhoea* in mice. VacciMonitor. 2009;18(2):76–8..