Cuban Meningococcal Vaccine VA-MENGOC-BC: 30 Years of Use and Future Potential

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ABSTRACT

Every year, meningococcal infection by *Neisseria meningitidis* causes over 500,000 cases and 85,000 deaths in the world, with 20% of survivors suffering sequelae. In Cuba its incidence in 1980 reached 5.9 cases per 100,000 population; about 80% of cases were serogroup B, prompting health authorities to declare meningococcal disease the country's main public health problem.

Several provinces reported over 120 cases per 100,000 children aged <1 year, overwhelmingly serogroup B. At that time, no vaccines existed with proven efficacy against *N. meningitidis* serogroup B, nor was there a vaccine candidate that could be successful in the short term. By 1989, researchers in Havana had developed a Cuban meningococcal B and C vaccine, VA-MENGOC-BC, the world's first against serogroup B meningococcal disease. Its efficacy of 83% was demonstrated in a prospective, randomized, double-blind, placebo-controlled field study. Vaccine production used vesicle or proteoliposome technology for the first time. The same year, the World Intellectual Property Organization awarded its gold medal to the main authors of the VA-MENGOC-BC patent.

The vaccine was used in a mass vaccination campaign and later included in Cuba's National Immunization Program, with a cumulative impact on incidence of serogroup B meningococcal disease greater than 95% (93%–98%). Mass, systematic vaccination shifted the spectrum of meningococcal strains in healthy asymptomatic carriers and strains circulating among population groups toward nonvirulent phenotypes. The disease ceased to be a public health problem in the country. VA-MENGOC-BC is the most widely applied vaccine against serogroup B meningococcal disease in the world. Over 60 million doses have been administered in Latin America. In several countries where it has been applied, in which strains other than the vaccine-targeted strains circulate, VA–MENGOC–BC has demonstrated effectiveness against all (55%–98% in children aged ≤4 years and 73%–100% in children aged >4 years). The vaccine and its proteoliposome technology have had an impact and continue to have potential, not only for meningococcal disease, but also for development of other vaccines and adjuvants.

KEYWORDS *Neisseria meningitidis*, meningococcal disease, meningococcal vaccine, biotechnology, pharmaceutical industry, bacterial meningitis, meningococcal meningitis, immunization, vaccination, Cuba

INTRODUCTION

Meningococcal disease, caused by infection with *Neisseria meningitidis*, has been greatly feared since the 19th century[1] and is still a global public health problem. Its main variants are meningitis and septicemia, both severe conditions and leading causes of invasive bacterial infection.[2]

Worldwide, annual incidence ranges from 1 to 27.5 per 100,000 population. During epidemics in the "meningitis belt" (Sub-Saharan African countries from The Gambia to Sudan), up to 1% of the population might become ill.[3,4] Overall case fatality is 5.3%–26.2%, with an average of 14.4%. During an epidemic in Africa, case fatality can exceed 30%.[5] Despite underreporting in many areas, it is estimated that there are over 500,000 cases and over 85,000 deaths every year. Twenty percent of survivors have sequelae, with risk in Africa triple that of the USA or Europe.[6]

There are millions of asymptomatic nasopharyngeal carriers of *N. meningitidis* in the world who can transmit the disease to others. Reported frequency is greatest in young adults (10%–35%).[7]

IMPORTANCE This article reviews development, characteristics, trials and use of the Cuban vaccine VA-MENGOC-BC, the world's first effective vaccine against serogroup B meningococcal infection, 30 years after its efficacy was demonstrated. The paper also describes its impact on population health in Cuba and other countries, especially in children and young people, as well as the contributions of its production technology to scientific and technological advances in the biotechnology industry.

In the 1960s, meningococcal disease was considered a public health problem only in tropical countries, but in the 1970s, this view changed with the appearance of outbreaks in Europe and North America. Since World War II, the main epidemics have been in Sub-Saharan African countries, including the meningitis belt, where 60% to 65% of all meningitis cases are meningococcal meningitis. However, meningococcal disease now occurs on every continent. Meningococcal disease caused by serogroup B meningococci occurs mainly in the countries of North America, central and southern Europe, southern and northeastern Africa, the Middle East, Russia, China, Japan, Australia and New Zealand.[3] During the early 1980's, when Cuba was just beginning vaccine development for later preclinical and clinical assessment, production and use, the country was a hot spot on the map of worldwide meningococcal disease burden, reaching an all-ages incidence of 14.4 cases per 100,000 population by 1984. After mass vaccination was instituted, beginning in 1989, meningococcal disease ceased to be a public health problem and Cuba no longer appears among the hot spots still found in other regions.

This article assesses the importance and current relevance of meningococcal disease in the world, its status in Cuba and results of the Cuban meningococcal BC vaccine, VA-MENGOC-BC, since its development. It analyzes, among other aspects, the impact of the vaccine's application, its current usefulness, relevance of its pioneering technology and its contribution to Cuban and global scientific development.

MENINGOCOCCAL DISEASE IN CUBA, VACCINE DEVELOPMENT AND USE

Meningococcal disease, characteristics and burden in Cuba: confronting and solving the problem From 1916 to the mid-

1970s, Cuba experienced only sporadic cases of meningococcal disease. In 1976, outbreaks began to occur that ballooned into epidemics. In 1978, incidence was 1.5 per 100,000 population and by 1979 it had reached 5.6 per 100,000 population. Over 50% of cases were caused by serogroup C and close to 35% by serogroup B. Most affected were children aged 10–14 years, followed by those aged <1 year.[8]

In 1979, Cuba undertook a vaccination campaign to control the disease; 3,245,046 people aged 3 months–19 years were vaccinated with meningococcal AC vaccine (Merieux, FR), for over 80% coverage. Incidence due to serogroup C decreased, but meningococcal disease continued to increase, and in 1980 reached 5.9 per 100,000 population; case fatality was 10%–25%,[8,9] and about 80% of cases were due to serogroup B. That year, meningococcal disease was declared the country's main public health problem. By 1984, overall incidence had risen to 14.4 per 100,000 population. Several provinces reported >120 cases per 100,000 children aged <1 year.[8]

At that time, no vaccine existed in the world with proven efficacy against serogroup B *N. meningitidis*, nor was there a vaccine candidate that could be successful in the short term. The highest development achieved by the most advanced groups was a serotype-specific antigen vaccine; its characteristics are summarized in Box 1 and compared with the Cuban vaccine.[9–12]

From 1980 to 1986, Cuban scientists at the National Center for Meningococcal Vaccine Development in Havana (precursor to the Finlay Vaccine Institute, founded in 1991), developed a vaccine candidate based on outer membrane vesicles (OMVs or proteoliposomes). Its clinical efficacy was field tested from 1987 to 1989. Developing this vaccine candidate involved creating a scalable and integrated production system with complex know-how for initial culture, fermentation, extraction, purification, formulation, adjuvantation, bottling and packaging. Stable OMVs were obtained, with a lipopolysaccharide composition apt for administration in humans without toxicity while conserving contribution to immunogenicity (Box 1).

With technological innovations in the development of VA-MENGOC-BC, patents were registered[13,14] that obtained licenses in Cuba[18] and, through the Patent Cooperation Treaty, in Australia and countries of the Americas, Europe, Asia and Africa. In 1989, the World Intellectual Property Organization awarded its gold medal to the main authors of the VA-MENGOC-BC patent. Their most important scientific achievements were obtaining immunogenic and stable OMVs or proteoliposomes from serogroup B meningococcus; the development process; and the product, whose composition, formulation and efficacy differed from existing vaccine candidates. Proteoliposomes or OMVs constitute the fundamental structure that ensures vaccine's immunogenicity and protective capacity. OMV characteristics are shown in Figure 1, and Box 2 describes the vaccine's formulation, as well as functions of the mixture and of several of the molecules formed.

Studies of the vaccine before licensing and mass administration From 1987 to 1989, a prospective, randomized, double-blind, placebo-controlled efficacy study was carried out in 7 provinces, involving 106,251 youngsters aged 10–16 years.

Box 1: Meningococcal B Vaccines Characteristics

Serotype-specific antigen vaccines (1970–1978)

Vaccines based on purified serotype-specific antigens, with adjuvants and without outer membrane vescicles (OMVs). Experimental formulations included capsular polysaccharides from other groups for better solubility. Lipopolysaccharide was mainly free or formed part of blebs or membrane fragments and had to be eliminated to the extent possible, due to its toxicity.

These were laboratory-scale efforts, lacking established technologies and good manufacturing practices. There was no demonstrated correlate of protection in controlled efficacy tests in humans. The few vaccines that were subject to trials in humans were discontinued. They required use of aluminum hydroxide as an adjuvant and to reduce toxicity.[9–12]

Cuban Vaccine VA-MENGOC-BC (1982–1989)

This is an OMV or proteoliposome vaccine. Its serological and overall efficacy is related to OMV presence, stability and consistency. The vesicular structure gives adjuvant and immunostimulating properties. OMVs provide the polysaccharide and other low immunogenic antigens with some degree of thymus dependence and enhance immune response to them.

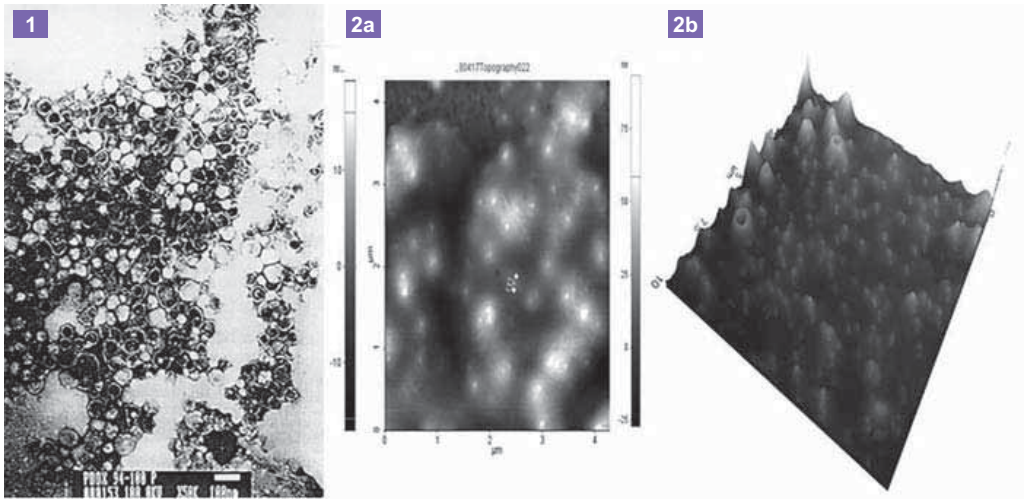
Lipopolysaccharide is integrated into OMVs and may or may not adsorb to $Al(OH)_3$ gel. VA-MENGOC-BC's adjuvant capacity does not depend on $Al(OH)_3$, but instead on OMVs, which also contain the proteins necessary for protection against a broad spectrum of heterologous strains.[13–16] The main role of $Al(OH)_3$ in VA-MENGOC-BC is to achieve pharmaceutical stability, which is supported by results with new formulations without aluminum hydroxide in preclinical development.[17]

Researchers from the Finlay Vaccine Institute, Cuba's Ministry of Public Health, Cuba's Center for State Control of Medicines and Medical Devices, PAHO/WHO, and the US CDC participated in discussion of the final trial protocol and its evaluation.

The field study lasted 16 months, during which 25 cases of meningococcal disease occurred. Once concluded, the blinding code was broken, revealing whether cases were in the placebo or vaccinated group: there were 4 cases among the 52,966 who received the vaccine, and 21 among the 53,285 who received the placebo. Estimated efficacy was 83% ($p = 0.0019$).[16] VA-MENGOC-BC thus became the world's first vaccine against serogroup B meningococcus found effective in a prospective, double-blind, placebo-controlled field trial.

In 1989, preclinical studies and phase I, II and III clinical trials required by national and international regulatory authorities were completed, and Cuba's Center for State Control of Medicines and Medical Devices—the Cuban regulatory agency—licensed VA-MENGOC-BC for marketing.[18]

Figure 1: Characteristics of VA-MENGOC-BC



Outer membrane vesicles of strain CU-B385/3 of serogroup B *Neisseria meningitidis,* basic core of VA-MENGOC-BC
Electron micrographs of proteoliposomes or outer membrane vesicles (OMVs). Vesicles 50–80 nm in diameter can be seen. Well-defined and chemically and physically stable OMVs or proteoliposomes are the heart of VA-MENGOC-BC and ensure its immunogenicity and protective capacity.
1) transmission electron microscopy
2a) two-dimensional atomic force microscopy
2b) three-dimensional atomic force microscopy. Digital Nanoscope III AFM (Santa Barbara, CA) coupled to scanner (J-Scanner) of 125 µm, Software used UTHSCSA Image Trial (USA).

Vaccination results from 1989 to 2019 With the vaccine registered, Phase IV (postmarketing surveillance) began. In 1989 and 1990, a national campaign was carried out, in which more than 3 million people aged 3 months–24 years were vaccinated, for over 95% coverage. High-risk groups were also included, mainly workers and students living in dormitories, prisoners, health personnel, etc., regardless of age, prioritized by province according to disease incidence.[8,16]

In 1991, VA-MENGOC-BC was added to the National Immunization Program, where it has remained without interruption or essential changes, using a 2-dose schedule, the first at age 3 months and the second at age 5 months. This universal and systematic immunization in infancy maintained coverage for those who were born after the mass vaccination campaign.

Annual incidence of meningococcal disease in Cuba before vaccination averaged 14.4 per 100,000 population. Following vaccination, the rate decreased to ≤1 per 100,000 population in 1993 and has remained below 0.1 per 100,000 population since 2008. In children aged ≤6 years, average annual incidence before vaccination was 38–120 per 100,000, and this dropped to 0.01–1.8 per 100,000 population in the following two decades. The reduction was an estimated 95% (93%–98%) and meningococcal disease has been eliminated as a public health problem in Cuba. [8,16,21–23]

Impact of mass vaccination on strain patterns in carriers and patients In the prevaccination epidemic stage, a cumulatively total of 96.8% of strains isolated from patients were from serogroup B, 1.4% from C, and 1.8% were not groupable. In carriers, 67.3% were from serogroup B, and 32.7% were not groupable. The vaccination campaign changed strain distribution: 100% of patients were now from serogroup B. In healthy carriers, strain distribution shifted to 26.7% from serogroup B and 70.8% from nongroupable strains, while serogroup W-135 appeared in 2.5% of cases.[24] Selective pressure by the vaccine, which was over 95% effective against group B (demonstrated by decreased incidence and reduced B capsule expression in healthy carriers from 67.3% to 26.7%) had not been previously described for any meningococcal B vaccine.

Changes in serotypes and subtypes in postvaccination patients and carriers can be interpreted as an expression of broad-spectrum vaccine-induced immune response, as epidemic serotypes and subtypes were eliminated or decreased and nontypable and nonsubtypable serotypes and subtypes increased in patients and carriers. Serotypes and subtypes different from the vaccine strain did not increase in patients or carriers. The vaccine was effective against homologous strains and also against heterologous strains.[24] Frequency and diversity of hypervirulent clonal complexes (ST-32 and ST-41/44) in patients and carriers decreased after vaccination and were replaced by the ST-53 complex, which represents a positive change. [25] After 2008, four serotype B:17 strains, never before reported in Cuba, appeared. Before this, between October 2004 and March 2005, strain B:17:P1.19, belonging to a new circulating clone (ST-269), was reported in Canada.[26]

These changes are favorable because two of the most important hypervirulent clones in the cause and expansion of Cuba's

Box 2: Additional characteristics of VA-MENGOC-BC
VA-MENGOC-BC is a bivalent vaccine of serogroups B and C meningococcal antigens, which forms a stable mixture adsorbed to $Al(OH)_3$ gel. Each dose contains 50 µg of membrane proteins, with 2 µg of serogroup B lipopolysaccharide, integrated in the OMVs, and 50 µg of serogroup C polysaccharide, as well as 2 mg of $Al(OH)_3$ gel, a formulation buffered with phosphates and sodium chloride at physiological pH; this mixture allows stable adsorption of the protein-polysaccharide-lipopolysaccharide complex, suitable for immune system delivery.

Proteomics has demonstrated the basis of its broad protective spectrum. Integration into the vesicles and adsorption to the gel detoxifies the lipopolysaccharide and assures conservation of its adjuvant properties, necessary in the formulation. OMVs constitute the fundamental adjuvant capable of provoking a potent Th-1 type immune response pattern.[18–20]

epidemic and others in the world were eliminated, in addition to the change in carrier phenotypes to nonvirulent variants and the transformation of epidemic strains in patients. However, it is necessary to carefully assess the possible importance of the appearance, although very limited, of clone ST-53, and whether the B:17 strains found are of the ST-269 type, as in Canada, as well as the levels of protection conferred by the Cuban vaccine against these strains.

Importance of immunization schedule and coverage in VA-MENGOC-BC's effectiveness Despite the 95% impact and protection achieved by the National Immunization Program's high coverage, as demonstrated over the past 30 years, there are indications that duration of postimmunization protection has decreased with the two-dose VA-MENGOC-BC schedule used in Cuba, particularly in children up to age one year. Although protection decreases over time, it was demonstrated that the vaccine was effective with the two-dose schedule and that it provides better protection against meningococcemia, which is more severe and lethal, than against the meningeal form.[27]

Decreased protection time with the program's schedule is due to the fact that bacterial vaccines' lower immunogenicity requires primary schedules of more than two doses, with boosters in the initial schedule[27] and even booster doses after a certain period or when the immune system is stressed. The superiority of a three-dose schedule for VA-MENGOC-BC has been demonstrated in studies conducted in Cuba and other countries.[16,28–30]

In conclusion, the vaccine could offer higher protection in infants and against the clinical meningeal form if an initial immunization schedule with three or more doses, along with a booster (which improves maturation of the immune response) were instituted; this should therefore be considered. However, even if the number of doses is increased, it is advisable to maintain the high coverage that has demonstrated effectiveness and sustained impact, and that will contribute to elimination of the disease.

ADMINISTRATION OF MENINGOCOCCAL HYPERIMMUNE GAMMAGLOBULIN (HGG) IN SEVERELY ILL CHILDREN

Participants in the vaccine registration clinical trials donated blood to obtain plasma, where vaccine-induced antibodies were in high concentrations. Globulins[31,32] were purified, their composition and concentrations characterized, and basic preclinical and toxicological studies performed.[32,33] Several lots of meningococcal HGG were produced and released by the national regulatory authority for experimental use in sick children whose lives were at risk.

Meningococcal HGG was used to conduct a clinical trial that included 123 children diagnosed with meningococcal disease in 21 intensive care units in 9 provinces.[31,32] For ethical reasons, results from the historical series were used as a comparison and meningococcal HGG was administered to all children in the trial.

Cases were stratified according to number of poor prognostic factors (PPFs). PPFs were established based on clinical assessment and disease course of patients in the epidemic's historical series. To evaluate effectiveness of meningococcal HGG administration, survival results in the clinical trial were compared with those with the same number of PPFs reported in the historical series.

Treatment followed established standards for patients with given numbers of PPFs, along with meningococcal HGG. In children with up to 2 PPFs, conventional treatment plus meningococcal HGG achieved 100% survival. With 3 or 4 PPFs, the respective survival percentages with conventional treatment were 86% and 78.5%, while in both cases survival was 100% with meningococcal HGG. Patients with 5 PPFs (serious, in clinical status terminology) had 53% survival with conventional treatment and 88.9% survival when meningococcal HGG was added. Children with 6 PPFs (classified as critical) had 21.4% survival with conventional treatment and 62.5% when meningococcal HGG was added. With 7 or 8 PPFs, administration of meningococcal HGG did not improve survival.

Certain combinations of PPFs had high case fatality and very low survival (20%) with conventional treatment, such as cases with a platelet count <150,000, + shock, + acidosis (pH <7.3). When meningococcal HGG was administered, survival increased to 62.5%. These results provided new evidence supporting the protective capacity of vaccine-induced antibodies.[31,32]

POTENTIAL OF VA-MENGOC-BC IN PREVENTION OF GONORRHEA

Two bacterial species of the genus *Neisseria*, *N. meningitidis* and *N. gonorrhoeae*, are antigenically related commensals and pathogens exclusive to humans. The first causes meningococcal disease and the second causes gonorrhea, a sexually transmitted infection. Gonococci have become resistant superbacteria and are a growing problem, with no vaccine to prevent them.[34,35]

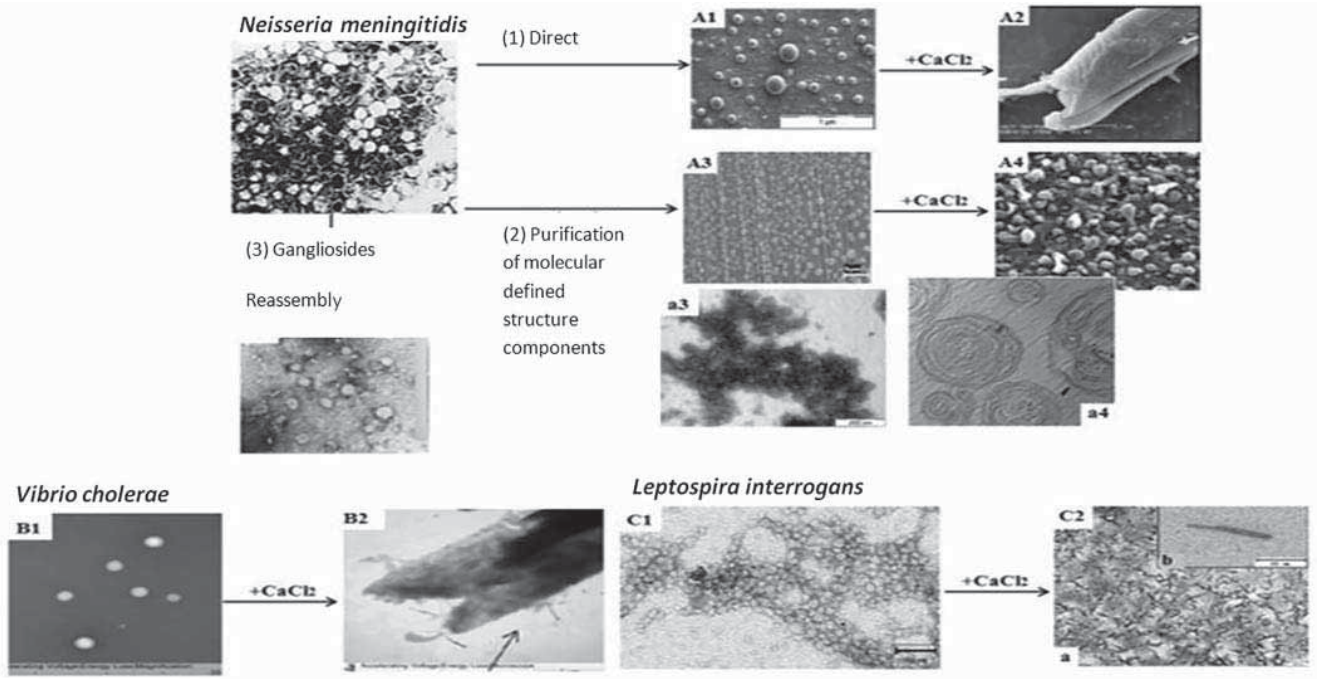
Laboratory studies conducted in Havana at the Finlay Vaccine Institute and the Pedro Kourí Tropical Medicine Institute (IPK) demonstrated cross reactions among *Neisseria* species antibodies in serum and secretions when VA-MENGOC-BC was administered to mice. Elements of a cellular response induced by VA-MENGOC-BC against gonococci were also identified, which could have contributed to the reduction of gonorrhea incidence after mass campaigns with this vaccine (at the time, there were also public health campaigns specifically directed at reducing sexually transmitted infections).[36]

In a case–control study conducted in New Zealand, those who received the meningococcal vaccine had a significantly lower risk of gonorrhea than those who were not vaccinated (OR 0.69, p <0.001).[37] Another New Zealand study with the same vaccine reported an overall effectiveness of 31% and a 47% effectiveness against hospitalization attributable to gonorrhea in one cohort.[38]

ADVANCES IN THE FIELD OF ADJUVANTS FOR HUMAN VACCINES: TECHNOLOGICAL PACKAGE AND PATENTS

The most widely used technological platform in Cuba for human vaccine adjuvants is based on proteoliposome technology to obtain OMVs from *N. meningitidis* strain CU-B385/3. This technology, which was used to manufacture more than 70 million doses of meningococcal vaccine, produced a family of patents, new vaccines and opportunities for biomedical and biotechnology development.

Figure 2: Platform developed using vesicular or proteoliposome technology



Electron micrographs of the adjuvant formulation platform with proteoliposome and cochlear structure, developed using technology from the Finlay Vaccine Institute, to obtain *N. meningitidis B* outer membrane vesicles (OMVs)
1) A,A1,A2 new OMVs and cochleates obtained directly from originals
2) A,A3,A4,a3,a4 a new generation of nano-OMVs and nanocochleates
3) very small size proteoliposomes with gangliosides, obtained directly from OMVs
The four photos in the lower block represent application of vesicular technology to cholera (B1,B2) and leptospirosis (C1,C2) vaccines.[39]

Table 1: Technology package. Know-how for new adjuvants and vaccines based on vesicular VA-MENGOC-BC technology

Document	Patent	PP	Biotechnology product(s)	Reference
CU 21888A1	X	—	Vaccine against *N. meningitidis* B	[13]
EP 0301992B1	X	—	Vaccine, gammaglobulin and transfer factor, *N. meningitidis*	[14]
WO 2004/047805A1	X	—	Cochleate-based vaccines and adjuvants	[40]
WO 2003/094964A1	X	—	Allergy vaccines and treatments	[41]
WO 2010/057447A1	X	—	Vaccines and types of administration	[42]
WO 2011/137876A2	X	—	Tolerogenic, malaria vaccines	[43]
WO 2002/45746A2	X	—	Poorly immunogenic antigen adjuvant (cancer)	[44]
Vaccine (1999)	—	X	Poorly immunogenic antigen adjuvant (cancer)	[45]
VacciMonitor (2012)	—	X	*Leptospira* nanocochleates and proteoliposomes	[46]
BMC Immunol (2013)	—	X	New *N. meningitidis* B vaccine, without $Al(OH)_3$	[17]
J Sci Tot Env (2019)	—	X	Meningococcal nanocochleates, nano-proteoliposomes	[19]
Rev Chim (2019)	—	X	Immunotoxicological evaluation vaccine without aluminum hydroxide	[20]
Methods (2009)	—	X	Proteoliposome & cochleates from *Vibrio cholerae* O1	[47]
BMV Immunol (2013)	—	X	*Bordetella pertussis* acellular vaccine	[48]

PP: primary publication

A new therapeutic allergy vaccine currently in clinical trials uses proteoliposome technology as an adjuvant. Therapeutic vaccines under development against several types of cancer also use variants of proteoliposome vesicular technology as adjuvants. The new generations of experimental meningococcal, leptospirosis, cholera and pertussis vaccines also use OMV technology in their production.[39] Figure 2 and Table 1 summarize these aspects.

OTHER SCIENTIFIC AND TECHNOLOGICAL ADVANCES MADE IN THE MENINGOCOCCAL VACCINE MACROPROJECT

Scientific and technological package, selected patents and publications Genetic engineering technologies were used to clone and obtain important proteins for new generations of serogroup B meningococcal vaccines: PorA, PorB, OpcA, NadA, Tbp, NspA, NlpB, lpdA, and others, and variants of some of these.[49,50]

Serogroup B polysaccharide peptide mimotopes were obtained and characterized by phage display technology, which opened new vaccine potential based on B polysaccharide and prevented possible development of autoimmunity.[51]

Table 2: Scientific technological package. Meningococcal vaccine macroproject's selected patents and primary publications

Document (year)	Patent	PP	Biotechnology Products	Reference
EP 0474313A2	X	—	P64k protein-r, carrier (cancer, infectious diseases)	[55]
WO 2009/003425Al	X	—	CIMAvax- EGF (cancer therapeutic vaccine)	[56]
CU 2006/0020	X	—	Mimetic peptides of *N. meningitidis* polysaccharide B	[57]
USP 5747653A	X	—	Hyperimmune gammaglobulin and its method	[58]
Int J Med Micr (2011)	—	X	Mimetic peptides of *N. meningitidis* polysaccharide B	[51]
Exp Rev Vaccines (2015)	—	X	CIMAvax-EGF-P64K (lung cancer therapeutic vaccine)	[59]
BBRC 308 (2003)	—	X	Dengue virus-P64k protein-r	[60]
Doctoral thesis (2006)	—	X	Human meningococcal immunoglobulin	[32]
Proteomics (2006)	—	X	Characterization of vesicles of VA-MENGOC-BC	[52]
Hum Vaccine (2009)	—	X	Characterization of vesicles of VA-MENGOC-BC	[53]
Microb Pathogen (1997)	—	X	Acquisition of *N. meningitidis* iron-regulated proteins	[49]
Biotecnología Aplicada (2008)	—	X	Genetic and immunological properties NlpB antigen	[50]

PP: primary publication

Table 3: Efficacy/effectiveness of VA-MENGOC-BC in populations and age groups of various countries

Place	Date	Age group	Efficacy /effectiveness by age group (%)		Reference
			≤4 years	>4 years	
Cuba (7 provinces)	1987–1989	10–16 years	—	83[a]	[16]
Cuba (12 provinces)	1988–1990	3 months–4 years	93	—	[61,62]
Cuba (14 provinces)	1989–1994	3 months–4 years	81	—	[62]
Cuba	1997–2008	<1 year	84	—	[27]
Brazil (Sta. Catarina)	1990–1992	3 months–7 years	66	88	[63]
Brazil (Rio de Janeiro)	1990–1992	6 months–9 years	64	82	[64]
Brazil (Sao Paulo)	1990–1991	3 months–6 years	55[b]	73	[65,66]
Colombia (Antioquia)	1991–1994	3 months–4 years	98	—	[67]
Uruguay (Canelones)	2002–2003	4–19 years	—	100	[68]
Uruguay (Montevideo)	2002–2003	4–19 years	—	88	[68]

[a]efficacy with placebo and vaccine in prospective, randomized double-blind design
[b]effectiveness in the prospective arm of study

Monoclonal antibodies against *N. meningitidis* were produced and are used for diagnostic purposes, in analytical techniques and in purification processes. Proteomics was used to study the CU-B385/3 strain, which contains in its OMVs all the proteins essential for protection against *N. meningitidis* with immunomodulatory power.[15,52,53]

Ultramicroanalytic ELISA-type assays were carried out—using small amounts of reagents and biological samples—for serological diagnosis of VA-MENGOC-BC–induced immune response in field studies, to evaluate population immunity, and to quantify concentrations of meningococcal immunoglobulin G from hyperimmune plasmas used in production of meningococcal HGG.[32]

The genetically engineered recombinant protein of *N. meningitidis* P64K was used as a carrier for vaccines, and its N-terminal is part of genetic constructs that enable high levels of fusion-protein expression. It is included in the structure of dengue vaccine candidates under development, and in therapeutic vaccines against cancer and autoimmune diseases. It is the carrier protein of CIMAvax-EGF, a therapeutic vaccine used in treatment of patients with lung cancer.[54] Table 2 summarizes patents and publications of this technological package.

VA-MENGOC-BC USE IN OTHER COUNTRIES

In several Latin American countries, strains different from VA-MENGOC-BC circulate, and VA-MENGOC-BC has shown a high percentage of effectiveness against all, in the range of 55%–98% in children aged ≤4 years and 73%–100% in children aged >4 years. Table 3 shows results of effectiveness evaluation in several countries, including Cuba.

In 1989–1990, 2.4 million children in the state of Sao Paulo, Brazil were given two doses of VA-MENGOC-BC. Effectiveness was lower than seen in Cuba, probably because isolated interventions were carried out without the rigor or systematic coverage of a campaign or program, in a state with more than 40 million inhabitants. Subsequently, other countries and regions within countries were incorporated, using two-dose vaccination schedules restricted to certain age groups, also with lower coverage than in Cuba, and where there was greater heterogeneity in circulating strains. In general, children from states, provinces or localities with high incidence rates were vaccinated in single interventions not included in a national immunization program, leaving children from neighboring localities and at-risk age groups unvaccinated.

Several reviews including studies of the efficacy of VA-MENGOC-BC against heterologous *N. meningitidis* strains in children aged ≤4 years demonstrate the effectiveness of the vaccine in these conditions.[69–71]

CONCLUSIONS

Meningococcal disease is no longer a public health problem in Cuba after the introduction of VA-MENGOC-BC vaccine, due to its structure (based on presence, stability and consistency

of proteoliposomes that confer immunogenicity and protective capacity) and administration strategy. VA-MENGOC-BC is the first vaccine of proven efficacy against *N. meningitidis* serogroup B and is also effective against C and a wide spectrum of heterologous serogroup B strains. It has cross reactivity against *N. gonorrheae*, which broadens the possible prevention spectrum for this infection. The vaccine's systematic application with wide coverage in Cuba's National Immunization Program keeps incidence of meningococcal disease low. Vaccination changes patterns of strains in asymptomatic carriers and circulating strains, which is important for the epidemiology of the disease. Greater survival in children with severe meningococcal disease treated with meningococcal hyperimmune gammaglobulin evidences the protective capacity of vaccine-induced antibodies. VA-MENGOC-BC production technology contributes to the development of the Cuban biotechnology and pharmaceutical industry, obtaining important technological advances, backed by a family of patents and primary publications in the field of vaccines and adjuvants, for current and future benefit.

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