Meningococcal Vaccines

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Abstract

Invasive meningococcal disease is a serious and global life-threatening disease. It affects more than 500.000 people worldwide annually, with 50.000 deaths and 50.000-100.000 severe sequelae, despite treatment. Six serogroups (A, B, C, W135, X, and Y) account for the majority of cases of meningococcal disease worldwide. Meningococcal polysaccharide vaccines were introduced several decades ago and have led to the decline in the burden of disease. However, these vaccines have several limitations, including poor immunogenicity in infants and toddlers, short-lived protection, lack of immunologic memory and herd immunity, and negligible impact on nasopharyngeal carriage. The conjugation of polysaccharide vaccines has the potential to overcome these drawbacks. Herein, we reviewed the new information about the quadrivalent conjugated meningococcal vaccines and meningococcal serogroup B vaccines.

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A. Meningococcal Epidemiology and Serogroups

Meningococcus has throughout the history been one of the most frightening infections causing recurrent epidemics all over the world. Meningococcal infection has a broad variance leading to asymptomatic carriage, occult bacteremia, sepsis, meningococcemia, fast-developing meningococcemia characterized by tissue loss (1). *N. meningitides* is one of the most common causes of meningitis and sepsis in children and adults all over the world. In parallel to the rise of pneumococcal conjugate and *Haemophilus influenzae* type b (Hib) vaccines to be included in the national vaccine calendars, *N. meningitidis* today is the most important cause of purulent meningitis. In a multi-centered study done by Ceyhan *et al.* in Turkey, it was found that meningococcus was on the top of the list with 56.5% in childhood acute bacterial meningitis (2).

In the United States of America (USA), 1400-3000 new cases diagnosed with invasive meningococcal diseases are reported annually (3). Morbidity and mortality of invasive meningococcal infections are still high despite early diagnosis and appropriate therapy. Although mortality is reported as 10-14%, it may reach the sequelaes rates of 20-40% such as deafness, convulsions, amputation and mental retardation. Annually 500 thousand invasive meningococcal disease cases and nearly 50 thousand mortalities are seen worldwide (4).

The most important characteristic differentiating meningococcia from other bacteria causing bacterial meningitis is that it can lead to epidemics. The only reservoir in meningococcal infections is humans. *N. meningitides* is carried nearly in 10% people's the upper respiratory tracts and transmitted from human to human through droplet spread. Meningococcal infections are common usually in children under two years old in developing countries and over ten years olds in industrialized countries (2, 5, 6). Some people are under greater risk for invasive meningococcal diseases. The most important factor is age and the disease is more prevalent in infants under one year old and adolescent and young adults aged 15-24. The peak incidence of the endemic disease is under 1 and 35-40% of

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the disease in children under 5 is seen in children under 1 (7, 8). Other factors generating predisposition for meningococcal diseases are living in over-crowded environments (such as boarding schools and military), poverty, smoking and exposure to smoking, having viral respiratory infections especially influenza, winter months and moving to a new social environment (9). Furthermore, sensitivity to meningococcal infections is defined whether there are IgG type antibodies developing against capsule polysaccharide. Complements also have an important role in bactericidal activity. Therefore, people with the lack of bactericidal antibody or lack ofhereditary terminal complement activity (C5-C9) and people with anatomic/functional asplenia, or lack of hereditary properdin or factor D have a higher risk ofmeningococcal disease respectively. The risk in people with the lack of properdin or lack of terminal complement is 250 and 600 times greater (10-12).

Thirteen serogroups have been defined leading to meningococcal diseases and the groups causing the most frequently diseases are A, B, C, Y, W135 and X. Serogroups may differ with regards to geographical regions and age groups (13, 14). While meningococcal infections are sporadically seen in developed countries, firstly group A and then W135-associated epidemics have long been known in meningitis zone in Africa (from Senegal to Ethiopia in Sub-Saharan Africa) (2, 15, 16). Apart from that, serogroup C-related epidemics have occurred especially among university students in England and North America (15). There occurred a Serogroup W135 epidemic during pilgrimage between 2000 and 2002 in Saudi Arabia and spread to other Muslim countries (2). Given the latest serogroup distributions commonly seen in different regions of the world are examined, while serogroup B and C are the factors of meningococcal infections in the continents of Europe and America, serogroup B in Japan and Australia and serogroup A in China and Africa are the dominant groups. Serogroup Y, one of the rare serogroups in recent years in North America and W135 are increasingly isolated more frequently in Muslim countries including Turkey sending pilgrims to Saudi Arabia. In fact, in a study done in the USA, it was found that while the rate of infections caused by serogroup Y in 1988 rose from 2% to 36% in 2007 (17).

Given the studies done with meningococcal serogroups in Turkey, it is seen that initially studies regarding nasopharyngeal meningococcal carriage in healthy people and then in the later years, studies serotyping in people who had invasive meningococcal diseases were carried out. It is observed that in the carriage studies locally carried out in various centers, the dominant serogroup has changed over the years (18). In a study done in Ankara in 1996, while serogroup B was the most common with 47.5%, it was found in two different studies in Istanbul in 1997 and 2000 that serogroup C (27.8%) and serogroup Y (53%) were respectively the common ones (19-21). Similarly, while it was found that the most common one was serogroup B (35.2%) in carriage in two studies done in Manisa in 2001 and 2002, serogroup W135 was the most common with 35.2% in 2005 in Istanbul (22, 23). First studies regarding the patients were done in Ankara and the most common serogroup was B with 32% in first studies (between 1974 and 1981), followed by serogroup A (20%) and C (16%) (24). In the second study (1987), on the other hand, it was reported that majority of the isolates were serogroup C (25). Given the results of a multi-centered meningitis surveillance study initiated by Ceyhan et al. in 2005, they found that *N. meningitides* was the in the first place among the pediatric bacterial meningitis agents between 2005 and 2012, and of the isolates in the 2005-2006 period, 42.7% were serogroup W135 and 31.1% serogroup B; in the 2007-2008 period, serogroup B was on the top of the list (35.1%), followed by serogroup W135 (17.6%); the dominant serogroup in 2009-2010 period was again W135 (56.1%), followed by serogroup A (36.6%), and in the 2012-2012 period, serogroup W135 (56.5%) was again in the first place. It wasproved by this study once again that the increase in genotyping and W135 stemmed from the transfer of the strains responsible for the epidemic in Saudi Arabia to Turkeyvia the Turkish pilgrims (2, 18, 26).

B. Meningococcal Vaccines

Polysaccharide vaccines have been developed tofight against meningococcal diseases and then since both the efficiency of these vaccines was insufficient and they were not be used in children under two, meningococcal conjugate vaccines have been developed. Since polysaccharide vaccines are not T-cell-dependent, they do not generate immunological memory and are not effective in children under two. Therefore, booster dose should be administered at intervals. In conjugated vaccines, polysaccharide antibody was bound to a carrier protein and converted into a T-cell and eventually it was enabled to be effective in infants and allowed the patient to be immune for a long time. Furthermore, nasopharyngeal carriage was decreased through conjugated vaccines and their contribution was observed to contribute to herd immunity. Since serogroup B has had immune tolerance towards polysaccharide in recent years, serogroup B vaccines have come into use with a non-capsular approach (17, 27).

***I. Polysaccharide vaccines*:** The first polysaccharide vaccine ever was licensed in the USA in 1974. Until today, one-valent (A and C), 2 valent (A/C) and for valent (A/C/Y/W135) have come into use. Currently, quadrivalent vac-

cines are in use; one is the Menomune® vaccine in use in the USA and the other one is Mencevax® licensed in Europe. Since the capsule polysaccharides inmeningococcai are the T-cell-independent antibodies, they only stimulate mature B lymphocytes. Therefore, they fail to generate the expected memory response in the case of encountering once again the T-cell-dependent memory response, long-term permanent antibodies and the same antibody again. The protective immunity reaches the level of 85-100% following the two weeks after vaccination. However, the antibody levels in children drop rapidly. It was proved that immunity against especially serogroup Ccould drop in recurrences. The immune response generated by these vaccines in children under two year olds is weak and therefore, cannot be used before two years ago. The protectiveness of polysaccharide vaccines in children under 5 years oldlasts for 1-3 years and in adolescents and adults for 3-5 years.Therefore, booster doses are needed.Additionally, these vaccines do not reduce carriage and fail to generate herd immunity. The undesirable side effects are rare and the most common side effects are local pains, irritability, headaches and exhaustion. Fever was reported in 2-5% of the adolescents. Today, conjugated vaccines are used instead of polysaccharide vaccines and the polysaccharide vaccinesare recommended only for people over the age of 55 who has meningococcal vaccine indication (28, 29).

II. Conjugated Vaccines: The infants under 2 years are the one of the age groups in which invasive meningococcal infections are the most common. The ineffectivity of polysaccharide vaccines in these infants has accelerated the development of meningococcal vaccines (30). The first meningococcal vaccine was the one-valent serogroup C vaccine and firstly went into use in England in 1999 (31). Subsequently, four valent vaccines composed of serogroup A, C, Y and W135 vaccines were developed (31, 32). Besides, different from the four valent vaccine, two valent (serogroup C and Y) vaccines were developed as well (31). Afterwards, serogroup C vaccine (Menitorix®) conjugated with Hib was licensed in the USA (33). At a result of the research carried out by the World Health Organization (WHO) and Program for Appropriate Technology in Health (PATH), conjugated meningococcal A vaccine (MenAfriVac®) was developed to be used in the countries in the African meningitis zone. The vaccine was used for the first time in Burkina Faso in 2010, and in Mali and Niger in 2011. Finally, Hib conjugated meningococcal serogroup C and Y vaccines were licensed (31, 33). The conjugated vaccines in use today are one-valent serogroup C, one-valent serogroup A and due to the difference of protein they are conjugated with, 3 different quadrivalent (A/C/Y/W135) conjugated vaccines are used. No meningococcal vaccine has yet been added to the routine vaccine calendar in Turkey.

1. Serogroup C conjugate vaccine (Menjugate®): It was included for the first time in the routine vaccine program in England in an attempt to control the epidemic and 76% remission was enabled in the prevalence rate of the vaccine in adolescents. It was revealed that the effectivity of the vaccine was 97% in adolescents and 92% if school age children and adolescents were considered together. Since carriage was reduced by 66% and the disease prevalence in unvaccinated people reduced by 67%, it was thought herd immunity could be enabled (34).

2. Serogroup A/C/W135/Y conjugate vaccines: There have so far been 3 kinds of quadrivalent (A/C/Y/W135) conjugated vaccines licensed to be administered to infants, children and adults and they are available in Turkey as well.

a*) MenACWY-DT conjugate vaccine (Menactra®)*: Menactra®, the first conjugated quadrivalent vaccine in the world, includes 4 meningococcal polysaccharides with each one covalently bound to diphtheria toxoid protein. It does not include adjuvant orprophylactics, and is administered intramuscularly (35). It was licensed in the USA in 2005 to be administered to 11-55 adolescent and adult age groups in order to prevent meningococcal diseases caused by serogroup A, C, Y and W135. Subsequently, age indication was firstly expanded to 2 years and it was approved for 9-23 months old infants by the FDA (Food and Drug Administration). It is recommended as a one dose for children above two years old, and two doses for infants aged 9-23 months with at least 3 month intervals (32, 33).

In pediatric studies done related to Menactra®, it was found that antibody levels gradually decreased, and especially the antibody levels of more than half of the 2 year-old childrenvaccinated one-dose dropped. It was also revealed that the antibody titers in adolescents did not drop; the antibody response in those given booster shot was higher than those in the serogroups shot for the first time except those in serogroup A (36, 37). There is no potential problem in using Menactra® together with other vaccines (measles-mumps-rubella vaccines, varicella, hepatitis A, 7-valent conjugated pneumococcus) with regards to efficiency and reliability. Despite the decrease in the antibody responses only against 3 of the 7 serotypes in the 7-valent conjugated pneumococus vaccine as a result of the combined use, the fact that the rate of children with protective level of antibody titres was over 98% does not make this decline clinically significant. Even though the side effects (fever and local reactions) are

more commonly observed, they are within acceptable limits. Moreover, after combined administration with other vaccines, no change was observed in the frequency of side effects (35).

Despite a decline in the prevalence of invasive meningococcal diseases following the use of Menactra® in the USA, it was seen that the diseases peak around the age of 18 continued. Therefore, while the Advisory Committee on Immunization (ACIP) in the USA recommended the routine administration of quadrivalent conjugated meningococcal vaccine to adolescents aged between 11 and 18, they decided that one booster dose be shot to adolescents vaccinated before 16 years old (38).

b) MenACWY-CRM conjugate vaccine (Menveo®): Menveo® was obtained by binding the C/W135 serogroups to CRM197 mutant diphtheria toxoide (non-toxic purified protein obtained from corynebacterium diphtheria) of capsule polysaccharides.It does not contain adjuvant orprophylactics, and is administered intramuscularly (39). It was licensed as one dose for people aged between 11 and 55 in the USA and Europe in 2010 and the age group was rearranged as 2-55 in 2011. Subsequently, European Medicines Agency (EMA) approved its use for those above 2 years old (with no upper age limit) in 2012; and the FDA in the USA approved the use of vaccine for infants in August 2013 basing their decision on the immunogenicity and reliance study involving 8700 infants. Accordingly, Menveo® was recommended 4 doses in 2, 4, 6 and 12 months during early infancy and 2 doses in 7th and 12th months in the late infancy period (33, 38, 39).

In studies in which Menveo® and Menactra® were compared, while no difference emerged with regards to immunogenicity and side effects between the two vaccines in children aged 2-5 and 5-10, and in adults, it was found that the antibody levels of over 1:8 obtained in adolescents for the serogroups A, W135 and Y vaccines were higher than those vaccinated with Menveo®. However, it is not known whether this difference is important with regards to clinical protection. No problem was found in combining Menveo® together with other vaccines (diphtheria, tetanus, acellular pertussis, Hib, inactive polio, hepatitis B); in fact, when it was used in combination with the other vaccine, 7-valent conjugated pneumococcus vaccine in which CRM_{197} was used as a carriage protein, no interaction occurred Similar symptoms to Menactra®were observed with regards to side effects (30, 40).

c) MenACWY-TTconjugate vaccine (Nimenrix®): The carriage protein of Nimenrix®, a quadrivalent meningococcal conjugate vaccine inclusive of polysaccharide serogroups A, C, W135 and Yis tetanus toxoide (41). The use of this vaccine was approved by EMA in April in 2012 to be used for in children under one year old and above and in adults. It is administered intramuscularly as a single dose to all approved age groups. Currently, the only quadrivalent conjugated vaccine to be used in 12-23 month-old infants in Europe is Nimenrix® (28).

Different from the two quadrivalent meningococcal conjugate vaccines, a new spacer molecule was used in A and C conjugation in Nimenrix®; the purpose of this was to increase the immunological response to these serogroups. It is because in the other studies done with the other two quadrivalent conjugated vaccines, it was found that antibody response related with serogroup A was lower than other serogroups (42). In a study in which Nimenrix® and Menactra® were compared, it was found that the percentage of cases whose protective antibody titres were 1:4 and 1:8 for serogroup A, Y and W135 was higher than those vaccinated with Nimenrix®. However, the effect of this difference on clinical protection is unknown (43). All the studies proved that the vaccine was well-tolerated in all age groups and that it had similar side effect profile with immunogenetical, other polysaccharide and meningococcal conjugate vaccines. Similarly, as it was the case with other conjugated vaccines, no interaction was observed in its combined use together with other childhood vaccines (30).

3. Serogroup A conjugate vaccine (MenAfriVac®): A serogroup-bound meningococcal epidemics are extremely common in African meningitis zone and epidemic-related mortality occurs more here compared to other parts of the world. Since quadrivalent meningococcal conjugate vaccines were more expensive, a serogroup A polysaccharide/ tetanus toxoid-protein conjugated vaccine developed through “Meningitis Vaccine Project” by WHO-PATH was started to be administered as a single dose to everyone aged 1-29 in December 2010 as part of a mass vaccination campaigns in Burkina Faso, Mali and Niger. According to the data obtained in Burkina Faso within this project, it was proved that serogroup A conjugate vaccine decreased the serogroup A-related meningococcal disease nearly 100%, eliminated the serogroup A epidemics on regional basis, caused decline in carriage and improved herd immunity (2, 44).

4. Hib-meningococcal serogroup C-Y conjugate vaccine (MenHibrix®): It is a combined vaccine that includes three different (Hib, meningococcal serogroup C and Y) capsule polysaccharides and uses tetanus toxoid for conjugation. It was approved by the FDA in June 2012 to be used in infants aged 6 weeks and 18 months in order to be protected from invasive Hib and serogroup C and Y-related meningococcal infections. ACIP recommended MenHibrix® for children with an increased risk

factor in this age group. The vaccine is recommended in six weeks the earliest and the last dose at 18 months old. Besides, it was reported that when the vaccine was administered together with other childhood diseases in 2, 4, 6, 12-15 months, there was a decline in its immunogenicity (33).

C. The Use of Meningococcal Vaccines (Indications)

When the recommendations by ACIP in the USA regarding the use of meningococcal vaccines are considered, there are fundamentally three groups targeted to be vaccinated. The first group includes those recommended to be vaccinated routinely; the second group is those with the risk factor of invasive meningococcal disease or those travelling to the regions where the disease is hyperendemic and the last group is the health personnel (33). While Menomune®, the polysaccharide vaccine, is the licensed vaccine in the USA, quadrivalent (A/C/Y/W135) conjugated meningococcal vaccines are Menactra® and Menveo®. Nimenrix® has a license in Europe (28).

Advisory Committee on Immunization (ACIP) recommends the meningococcal vaccine to be routinely administered to the adolescents aged 11-18. Since the biggest age group in which invasive meningococcal disease is most common in the USA is the adolescents, it is recommended that the first dose is routinely administered at 11-12 and the second dose at 16. In case the first dose is not administered at 11-12, the first dose is recommended at 13-15 and the second dose at 16-18; those who are given the first dose at 16 or over, are not recommended a booster dose. Besides, the university students who were not vaccinated at the 11-18 period and will stay at the university dormitory are recommended a single dose (33, 38).

Advisory Committee on Immunization (ACIP) recommends the vaccine for those with a risk of invasive meningococcal disease from 9 month on (those lacking persistent complement component, those with anatomic or functional asplenia, soldiers-military personnel, HIV-infected people, those wishing to minimize the risk of their meningococcal disease or controlling meningococcal epidemics or those travelling to the regions where the disease is hyperendemic. Besides, since children with asplenia have invasivepneumococcus infection risk, Menactra®, conjugated meningococcal vaccine which includes diphtheria toxin also available in the conjugated meningococcal vaccine should not be administered to children under 2 years old in order for the immune response not to degenerate against the pneumococcus vaccine (33).

The health personnel are not recommended the routine administration of meningococcal vaccine. Those with the risks mentioned above or the health personnel travelling to the regions where the disease is hyperendemic for work/visit are recommended the conjugated meningococcal vaccine. Besides, the microbiology laboratory personnel dealing with meningococcal isolates are also recommended the vaccine (33, 38).

Lastly, regarding the booster dose of the children whose polysaccharide or meningococcal conjugate vaccination is complete, but who continue to pose a risk interms of meningococcal disease, the following booster dose vaccination recommendation is made; to children aged 2-6, 3 years later after the first vaccination; to children and adolescents aged 7-10, 5 years after the first vaccination. Those administered two doses of primer vaccination should be shot a booster dose after 5 years. Besides, as long as the risk continues, booster doses should be repeated every five years (28, 33, 38).

Table 1 illustrates the countries that have included meningococcal conjugate vaccines into their national vaccination calendars, the target group of children and vaccination schemas (33, 45-48).

D. Serogroup B Meningococcal Vaccines

Since polysaccharide capsule of Serogroup Bhas a great similarity with the polysaccharide epitopes of neural cell adhesive molecule glycoproteinsin human nerve tissues, it has an immune tolerance to serogroup B capsule. If the structure of polysaccharide in serogroup B capsule is changed in order to eliminate immune tolerance, this time the risk of triggering autoimmunity in humans occurs. Therefore, the use of external structure of capsules due to their antigenic characteristics was considered; and similarly, the development of vaccines in which outer membrane vesicles (OMV) and outer membrane proteins were used were considered as well (28).

I. OMV Vaccines: Strain-specific OMV vaccines were developed in order to control serogroup B clonal epidemics and were used to stop the spread of serogroup B epidemics extending all the way to Cuba, Norway, France, Brazil, Chile and New Zealand. In conclusion, protection rates varying between 57% and 94% were obtained. However, the most important limiting handicaps of OMV vaccines are that they generate strain-specific protection and that they fail to generate cross-protection against other strains especially in infants (28, 31, 49).

II. Quadrivalent Serogroup B Vaccine (Bexsero®): In an attempt to develop non-strain-specific serogroup B vaccine by specifying the protected proteins expressed on the meningococcus surface, some genomic studies termed as “reverse vaccinology” were carried out. As a result, (in addition to the OMV and the inclusive porin A

Table 1. Countries that added meningococcal conjugate vaccine in their routine vaccine calendar

Countries	Conjugated serogroup C vaccine	Conjugated serogroup ACWY vaccine
The USA		• 11-12 years first dose and 16 years second dose • If the first dose shot at 13-15 second dose at 16-18 • >16 years one dose • One dose to students aged between 19-24 staying in dormitory
Canada	• In frequently seen regions, 3 doses with one-month interval beginning from 2nd month • All infants and children aged 1-11, one dose (12th month on the calendar)	• At 12 years one dose regardless of the previous vaccination history
Austria	• 12th month one dose	• 12 years one dose
Belgium	• 15th month one dose	
Southern Cyprus	• 12th month one dose	
France	• Between 1-24 years one dose	
Germany	• Between 11 months-17 year one dose	
Greece	• In the 2nd, 4th and 6th months 3 doses	• Between 11-18 years one dose
Island	• In the 6th and 8th months 2 doses	
Ireland	• In the 4th, 6th and 13th months 3 doses	
Italy	• Between 13-15 months one dose • Between 11-18 years one dose if not vaccinated before	
Liechtenstein	• Between 12-14 months one dose • Between 11-15 years one dose if not vaccinated before	
Luxembourg	• In the 13th month one dose	
Holland	• In the 14th month one dose	
Portugal	• In the 12th month one dose	
Spain	• In the 2nd month, 12th month and 12 years 3 doses in total	
England*	• In the 3rd month, 12th month and 14-15. Years 3 doses in total	
Australia**	• In the 12th month one dose	
Saudi Arabia		• <6 months and <2 years: 2 doses with at least 3-month intervals • 2-5 years: One dose
The United Arab Emirates		• At 11-12 years first dose and at 16-18 years second dose

*The vaccine shot in the 12th month Hib-MenC combined vaccine
**The vaccine administered Hib-MenC combined vaccine

obtained from the epidemic strain in New Zealand), a vaccine that included three major antigens (factor H-bound protein, recombinant neisseryal adezin A andneisseryal heparin-bound antigen) was developed. The serogroup B strains coverage of the vaccine was investigated in different countries by the Meningococcal Antigen Typing System (MATS) test which could be implemented in a limited number of reference laboratories in the world. Based on these analyses, the coverage rate of Bexsero vaccine varies between 66% and 91%. It is possible to collect the strains in our country and get them analyzed by MATS; in order to do this, it is primarily crucial to strengthen the meningococcus surveillance. However, if this is not possible, the data of the neighboring countries can be used for coverage. It is also promising that there are data available suggesting that this vaccine also generates cross-protection against other serogroups apart from the serogroup B. The vaccine was administered to all age groups beginning from two-month-old infants and studies revealed that it was well tolerated and immunogenetical. The vaccine was approved in January, 2013 by EMA to be used in Europe, and was recommended to be included

into the national vaccine calendar in England in March 2014. Its usage;three doses with one-month interval between shots in infants aged 2-6 monthsand one booster dose between 12-23 months; two doses with at least two-month intervals in infants aged 6-11 months and one booster dose at the age of 2 with at least two-month intervals between the primer series and the booster dose; two doses with at least two-month intervals in infants aged 12-23 months and one booster dose at the age of 2 with at least two-month intervals between the primer series and the booster dose; two doses with at least two-month intervals between the ages of 2-10 and two doses with at least one-month interval in children over 11 years old. While the most common local and systemic side effects in infants and children are sensitivity on the vaccination site anderythema, fever and delicacy, in adolescents and adults, they were pain on the vaccination site, weakness and headaches. Besides, the infants were administered the vaccine together with other routine vaccines, it was reported that the level of fever was higher (32, 49, 50).

Bexsero has so far been used more than 500 thousand doses in European Union countries, Canada and Australia It was included in the routine vaccine calendar in England as of March, 2014 with the total of 3 doses on the 2nd, 4 and 12th months (51). It was decided in the Basilitica region of Italy that it would be administered as three doses in infants and would be shot as a booster dose on the 13th month (52). In Poland, clinical recommendations are made to administer the vaccine to infants, children and adolescents beginning from the 2nd month (53). More than 35 semi-public insurance providers in Germany agreed to cover the cost of Bexsero for all voluntary children aged between 2 months and 18 years (54). In Australia, infants under two and adolescents aged between 15 and 19 are recommended the Bexsero vaccine and the vaccine is about to be included in the routine vaccine calendar (55). In the Czech Republic, on the other hand, the Czech Vaccine Academy recommends Bexsero for children aged between 2 and 10, adolescents aged 13 and 15, and the individuals under great risk (56).

III. Other Vaccines inclusive of Outer Capsule Antigenic Structures: The studies regarding the recombinant vaccine named as LP2086 inclusive of two meningococcal factor H-bound protein variant have still been underway. It has been reported in Phase II studies that the vaccine is immunogenetical and well-tolerated (28, 30).

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