IS EFFECTIVE BEXSERO FOR INVASIVE MENINGOCOCCAL DISEASE PREVENTION ?

FINAL DEGREE PROJECT

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ABSTRACT

INTRODUCTION: Invasive Meningococcal Disease (IMD) is considerated as a Major Health Problem and it causes substantial morbidity and mortality. It is caused by *Neisseria Meningitidis*. This pathology especially affects children under 5 years old and teenagers, although it can occur at any life stage. In fact, in our environment *N. Meningitids* is the first cause of bacterial meningitis in children > 3 months, and specifically *N. Meningitids* serogroup B is the most usually involved. Recently, a new vaccine called Bexsero has been deveolped and commercialised for IMD prevention due to serogroup B. However, the use of that vaccine is highly controversial because few information about its effectiveness is available. Even so, paediatricians as well as organisations like "Comité Asesor de Vacunas" encourage parents to vaccinate their children with Bexsero.

OBJECTIVE: this study aims to assess the effectiveness of Bexsero for Invasive Meningococcal Disease prevention in children under 5 years old. Moreover, the study will provide useful information about the possible association among being vaccinated with Bexsero and have a greater proportion of adverse reactions.

DESIGN: This is an observational prospective cohort study.

METHODOLOGY: In this study we will have two groups: vaccinated with Bexsero (cohort 1) and Unvaccinated with Bexsero (cohort 2). Then, we will perform a 5 years follow-up and we will compare the incidence of IMD registered in both groups. We will expect a significant reduction in incidence of IMD in children that have been vaccinated.

KEY WORDS: Invasive Meningococcal Disease, Meningococcus, *Neisseria Meningitidis*, Bexsero, effectiveness.

ABBREVIATIONS

IMD: Invasive Meningococcal Disease

SIRS: Systemic Inflammatory Response Syndrome

MD: Meningococcal Disease

MM: Meningococcal Meningitis

MS: Meningococcal Sepsis

DIC: Disseminated Intravascular Coagulation

CNS: Central Nervous System

CSF : Cerebrospinal Fluid

PCR: Polymerase Chain Reaction

CRP: C Reactive Protein

INTRODUCTION

BACKGROUND

1. DEFINITION

Invasive Meningococcal Disease (IMD) is a severe, life threatening infectious illness caused by *Neisseria Meningitidis.* [1–3]

There are two main clinical forms of IMD described: [1,3]

Meningitis: which is an inflammatory process of the leptomeningeal membranes that overcoat the central nervous system (CNS). It is considered as a medical emergency, therefore prompt diagnosis and treatment should be performed when it is suspected.[4]

Sepsis: its definition has been controversial over the years. Nowadays, we define sepsis as a systemic inflammatory response syndrome (SIRS) caused by local or disseminated infection. [5]

Meningococcus can also produce other clinical manifestations, that are less frequent, such as pneumonia, arthritis, endophthalmitis, pericarditis, osteomyelitis, otitis, cellulitis, sinusitis and chronic meningococcemia. [6] These manifestations are not considered IMD, so they will not be explained on the present protocol.

2. RELEVANCE

Certain aspects of meningococcal disease have led to consider it as a major health problem, even today.
These aspects are: its global distribution, its epidemiological pattern, their high mortality rates, the impact it has on the quality of life in patients who survive and their families due to the sequelae they suffer, and that the most affected population groups are children under 5 years old and teenagers. [2,7–9]

In our environment, meningococcus is the first cause of bacterial meningitis in children under 3 years old and the second one in adults. [9] Moreover, *N. Meningitidis* is, still today, the first cause of sepsis during childhood. [5]

Mortality associated with meningococcal disease is high, ranging from 10%-14%. It can also produce major sequelae in those who survive in 20%-30% of cases. Those complications

include: loss of limbs, deafness or hearing loss, blindness, brain damage with mental retardation, epilepsy and seizures, hydrocephalus, renal failure and cutaneous scars. [3,6,9]

Mortality is linked to several factors such as clinical form (sepsis has higher mortality than meningitis), age of the patient (it increases with age) and microorganism serogroup.[9]

Finally, MD and its complications have an important socioeconomic impact in our country. [3] IMD causes a hospitalisations rate of 2.33 / 100.000 hab per year and an associated direct cost of more than 5 million € in mortal cases. For survivors there is an important reduction of life quality and an economic cost of millions of euros due to major sequelae.

3. EPIDEMIOLOGY

Meningococcal disease is distributed worldwide, but with important differences between geographical areas. [1,6,10,11]

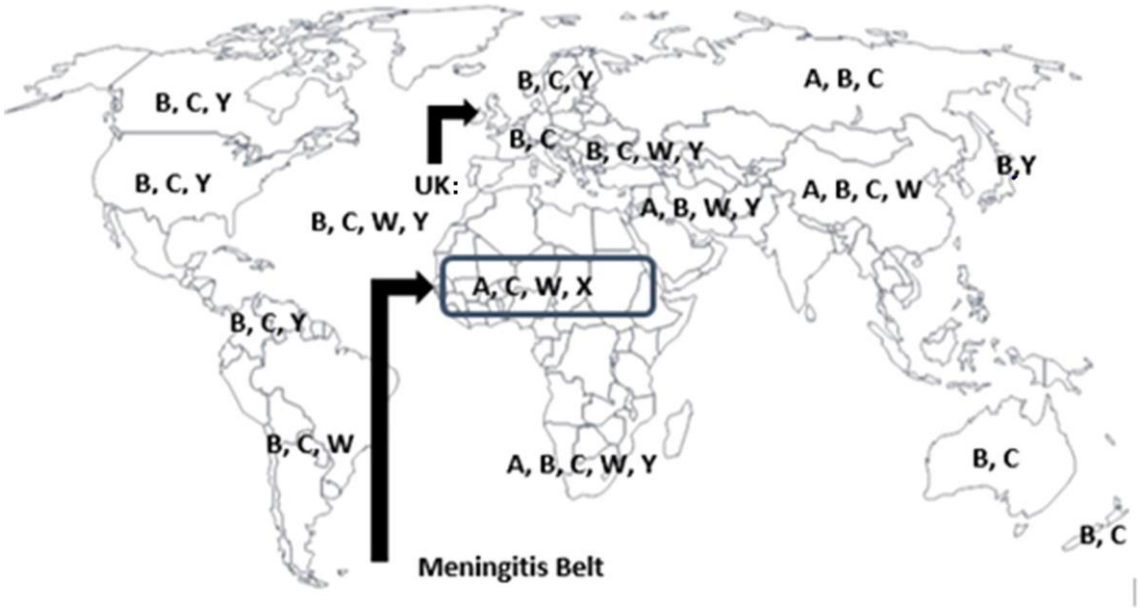


Figure 1. Map of the predominant *N. Meningitidis* serogroups by geographic location from [1]

This disease has an epidemiological pattern that combines sporadic or endemic cases together with epidemic outbreaks. [1,2]

Part of the explanation for this behaviour seems to be related to the different serogroups of *N. Meningitidis* identified and their geographic distribution across different regions all around the world. [1,8,12]

According with several elements contained in the polysaccharide capsular structure, 12 serogroups have been identified. However, mainly 6 of them cause the vast majority of the disease. [1]

Serogroups identified: A, B, C, E, H, I, K, L, W, X, Y and Z.

Serogroups that cause IMD: A, B, C, W, X and Y.

The characteristics of the most important serogroups are: [8,12]

Serogroup A: is basically responsible of big epidemic outbreaks that occur in a region of Africa known as "Meningitis Belt".

Serogroup B: is usually involved in large epidemic waves combined with long interepidemic periods during which it can produce sporadic cases.

Serogroup C: it produces short epidemic waves. Nowadays, due to massive vaccination campaigns its incidence has declined. [8]

Other factors involved in epidemics development are not well stablished yet. [1,10]

Globally, it is estimated that there are more than 1.2 million cases and more than 135,000 deaths annually, but the real number of cases could be higher since some countries don't have a surveillance system. [1,2]

The epidemiological situation in Spain, as well as in other European countries, is characterized by the following: [1,2,8,10,13,14]

- The main responsible serogroups in most IMD cases are B and C. During 2014-2015 there were 206 confirmed cases of IMD in Spain, which means an incidence rate of 0.53 confirmed cases/100.000 hab. From those cases, 69% were caused by serogroup B; whereas 10% were due to serogroup C.
- Cases due to serogroup C have declined since conjugated vaccine against this serogroup was introduced in routine vaccination schedule.
- Historically, serogroup B has been and is the main cause of IMD (**Annex 1**).
- The most affected population groups are: children under 5 years old (2.18 cases/100.000 hab) and especially children less than 1 year (8 cases/100.000 hab) followed by teenagers among 15 – 19 years old (**Annex 2**).
- Highest mortality rates are observed among adult population.
- Carriers rate is highly variable ranging from 8%-10%. Highest rates are observed in teenagers, where it arrives till 25%.

D. Moreno *et al* [15] show in their work that Spain has an incidence rate of IMD due to serogroup B superior than European average. In fact, it is the fifth country with highest incidence rates of the European Union. By absolute number of cases, Spain is the third country behind United Kingdom and France.

Data about epidemiology of IMD in Europe are graphically represented in **Annex 3**.

4. EPIDEMIOLOGICAL CHAIN [4,9,16]

Pathogen Agent:

- Neisseria Meningitidis is a bacteria that only infects humans, who are the main reservoir.
- Its natural environment is the epithelium of human nasopharynx.

Transmission Mechanism:

- It is required a close contact between a healthy human and a carrier or, less commonly, with a sick person.
- The transmission is mediated by contaminated secretions that are produced by infected people and inhaled by healthy people.

Transmisson Period:

- Humans can transmit meningococcus until the bacteria disappears from their nasopharyngeal secretions.
- After starting a properly treatment an infected person can infect others for 24 hours.

Incubation Period:

- There is a period of 2 to 10 days between the infection and the development of symptoms, if they appear.
- In the vast majority of people the incubation period lasts 3-4 days.

5. RISK FACTORS

No everyone who is exposed to *N. Meningitidis* develops an IMD. Both bacterial and host factors are involved in the development of the disease. [1]

Factors related with microorganism will be discussed in the following section.

Factors related with the host are:

- **Age**: As it has been said in the epidemiology section, several groups of population are at major risk to develop IMD according to its age. The reasons that explain that fact are [1]:
  - Infants less than 1-year-old: due to a decrease of maternal antibodies and an immature immune system, there is less immunity against meningococcus and other pathogens at that age group.
  - Children under 5 years old: at that age, the immune system is not competent enough to detect and fight against capsulated bacteria such as *N. Meningitidis*.
  - Teenagers: in that population group factors involved in development of IMD are high carriers rate and risky behaviours such as close contact between them. [17]
- **Persistent complement deficiencies**: people with deficiencies of C3, C5-9, properdin, factor D and factor H are more vulnerable to develop IMD. The complement system is composed by a group of proteins that recognise the bacteria and help the immune system to destroy it. Hence, people with defects in that system are unable to destroy *N. Meningitidis* effectively, so it is easier for the bacteria to reach the CNS causing a meningitis or reaching the bloodstream producing a sepsis.[1]
- **Primary and secondary immunodeficiencies**: Those who cannot produce an adequate humoral response are at major risk of developing more severe and unusual forms of IMD. A special mention has to be done in patients with HIV infection, because the risk of having an IMD is related with low CD4 number or development of AIDS and not only with the HIV infection itself.[1]
- **Anatomical or functional asplenia**: Spleen is an organ who helps the host to fight against capsulated bacteria, as meningococcus. So, people who have a splenectomy or diseases that can affect its function (for example sickle-cell anaemia) are at greater risk to develop IMD as well as other infectious diseases.[1]
- **Genetics**: some studies point that they exist genetic polymorphisms which could be associated with development of invasive disease, although its role has not been stablished yet. [1]

To conclude, some environmental aspects are also important [1,3,17]:

- **Job**: Working with samples that contain *N. Meningitidis* increases the possibilities of suffer an IMD.
- **Close contact** with infected people or carriers.
- **Living** or **travelling** to high endemic regions.
- **Smoking**: it has been reported that people who smoke have more IMD.
- **Season and previous viral infections**: Peaks of IMD are seen during winter months, probably related with previous viral respiratory infections.

6. MICROBIOLOGY

The microbiological structure of *N. Meningitidis* determines its ability to produce the different clinical forms we observe. [7,12]

The virulence of meningococcus is provided by the following: [2,7,17]

- Polysaccharide capsular structure: it protects the bacteria from phagocytosis thus allowing it to survive in the bloodstream. It is probably, the most important virulence factor of meningococcus. In fact, in IMD cases we usually identify capsulated bacteria, whereas asymptomatic carriers usually have non capsulated bacteria in their nasopharynx. [2,12]
- Outer membrane: contains protein complex called *pilli*. These structures allow meningococcus bind to the epithelial cells of the hosts nasopharynx and promote bacterial growth.
- Endotoxin: is the main responsible of the clinical features, particularly meningococcal sepsis, which is explained with more detail in the following section. It is a lipopolysaccharide that produces a systemic inflammatory response.

7. PATHOGENESIS OF CLINICAL FORMS

The interaction between host factors and microbiological aspects explained in previous sections determines the following clinical forms:

Carriers: The host immunity controls the bacteria, so the person becomes a carrier without developing symptoms. However, he can spread the disease and infect other people. Carriers rate changes widely for factors not well understood, although an increase on the number of carriers seems to be related with more risk of an epidemic outbreak. Being a carrier makes the person immune against meningococcus, but it is not well stablished for how long. [2,4,9]

Forms of IMD: The bacteria, for reasons that still remain unknown, overcomes the natural defense barrier reaching the bloodstream. Then, by haematogenous dissemination it arrives to several structures and causes an IMD.

Meningococcal meningitis (MM): is produced when meningococcus reaches some particular regions of the CNS, that are more vulnerable, such as choroid plexus and cerebral capillaries, through which the bacteria arrives at subarachnoid space and produces an infection of the CSF causing an inflammatory reaction. This reaction activates glial cells, who start to produce proinflammatory mediators and activates the immune response. Finally, the inflammation produces cerebral swelling and increases the intracranial pressure. Meningitis may or may not be accompanied with meningococcal sepsis. [4,17]

Meningococcal sepsis (MS): is due to an uncontrolled and exaggerated inflammatory response produced by meningococcal endotoxin, who stimulates a massive liberation of proinflammatory mediators such as cytokines and interleukins and also activates the coagulation process into the blood vessels. This systemic reaction has negative consequences as systemic vasodilation, increased capillary permeability and haemodynamic instability. All that, can lead the patient to an acute shock state with multiorgan failure and death in a few hours. [2,4,17]

8. SIGNS AND SYMPTOMS

IMD could be clinically manifested as: [17]

- Meningitis alone: 15% of children.
- Septicaemia alone: 25% of children.
- A combination of both: 60% of children.

Although the most common is a mixed process with meningitis and sepsis, we usually use meningitis when it is the unique or the main clinical manifestation; while we use sepsis when systemic symptoms are the most important or there is not meningitis. [2]

MENINGOCOCCAL MENINGITIS

Clinical presentation of MM does not differ significantly from other meningitis caused by other pathogens. In fact, at primary stages of the disease it can be easily confused with non-severe processes as viral infections. [18]

On the contrary, there are important differences according to the age of the patient. Hence, it is necessary distinguish between typical symptoms of infants from those of children or teenagers, who have similar manifestations as adults. [18]

- Infants: newborns and infants less than 1 year usually have unspecific symptoms like irritability, food rejection, inconsolable and acute crying, convulsions, apnea and bad general condition. They usually do not have fever. Some specific signs as bulging fontanelles and macrocephaly are not very common and appear later. [4]
- Children: classic signs and symptoms include high fever, chills, vomiting, severe headache, altered level of consciousness, leg pain and, less commonly, convulsions or other neurological focalities such as photo or phonophobia. In the physical exam Kernig's and Brudzinski's signs or stiff neck are highly suggestive of meningitis, but they appear in advanced stages of bacterial meningitis. [2,4,17,18]

A widely described as a major sign of meningococcal disease are petechial eruptions on the skin. Although they are highly related with this illness, not all patients show it. [18]

MENINGOCOCCAL SEPSIS

Clinical manifestations usually include sudden peaks of fever, vomiting, joint pain, muscle pain and cutaneous exanthema (petechial, maculopapular or equimotic). [2]

If it is left to evolution, it can cause a septic shock state with hemodynamic instability. [5,18]

A special form of meningococcemia is Waterhouse-Friedrichsen Syndrome. It is a fulminant sepsis with fast and catastrophic evolution including haemorrhagic cutaneous lesions, DIC, shock, multiorgan failure and even death in less than 24 hours, although we start a properly treatment. That condition is developed when there is a massive bleeding into the adrenal glands, so they stop functioning. [4,6,18]

In the following box there is a summary of signs and symptoms of MM and MS: [2,17]

	MM	MS
More specific signs & symptoms	❖ Petechial rash that do not disappear with pressure (it is present in 28%-78% of patients at admission) ❖ Bulging fontanelle in babies ❖ Stiff neck, Kernig's and Brudzinski's signs ❖ Altered mental state ❖ Seizures ❖ Photophobia	❖ Leg pain ❖ Non blanking rash ❖ Signs of shock: • Altered mental state • Capillary refill time >2 seconds • Cold peripheries • Unusual skin colour • Tachycardia • Oliguria • Hypotension (late sign)
Less specific signs & symptoms	❖ Fever (present nearly in 100% of patients) ❖ Reduced oral intake ❖ Vomiting/nausea ❖ Lethargy ❖ Irritability ❖ Ill appearance ❖ Headache ❖ Muscle or joint pain Less frequent ❖ Diarrhoea ❖ Coryzal symptoms (common cold symptoms) ❖ Sore throat	❖ Fever (nearly present in 100% of patients) ❖ Vomiting / nausea ❖ Lethargy ❖ Irritability ❖ Reduced oral intake ❖ Chills / shivering

9. DIAGNOSIS

Given the relevance of IMD prompt diagnosis is required in order to make an appropriate treatment and improve patient's prognosis. [2,9,20]

In this disease, we can have suspicious cases, probable cases and confirmed cases. [9,16,20]

Case: patient with a combination of signs and symptoms suggestive from meningitis or sepsis.

Suspicious Case: case with clinical features described before where meningococcus is the most probable etiologic agent without any laboratory test performed yet.

Probable Case: case with clinical features where we have identified Gram negative diplococci in usually sterile sites or in petechial fluid samples.

Confirmed Case: case with clinical features that accomplishes one of the following criteria:

- Isolation of *N. Meningitidis* from usually sterile sites such as blood or CSF or in petechial fluid.
- Detection of *N. Meningitidis* DNA from a formally sterile site or purpuric skin lesions.
- Detection of *N. Meningitidis* antigen in blood, CSF or urine.

First, the identification of suspicious cases is based on recognising signs and symptoms of the patient. However, as we have seen, clinical manifestations can be widely unspecific, constituting a big challenge for paediatricians and health practitioners in general. [2]

In fact, according to a clinical practice guidance made by the Health Ministry, only 50% of cases are diagnosed during the first admission in Primary Care Centres or in Emergency Rooms of Hospitals.[2]

Secondly, to classify a patient as probable or confirmed cases, it is necessary carry out some complementary tests.

However, it is important to notice that under suspicion of meningococcal disease an antibiotic treatment and supportive care have to be stablished as fast as possible, due to its unpredictable evolution and potentially fatal consequences. Delaying treatment for testing or clinical revaluation is not warranted. [2,4,5]

10. COMPLEMENTARY TESTS

The following complementary tests must be performed under suspicion of an IMD case to confirm it:

- **Cultures**: they allow isolation of *N. Meningitidis* from sterile sites. Cultures can proceed from blood, CSF or petechial fluid. However, they have an important limitation because if the patient has received antibiotic treatment before we obtain the sample, their result can be falsely negative. [2,18,20]

Hemoculture: Historically, and still today several authors argue that hemoculture is the standard reference procedure to confirm an IMD. However, recent advances in new diagnosis techniques are changing that fact. The most substantial change has been PCR development. [2,20]

- **Lumbar puncture**: in meningitis cases it must be performed unless any contraindication exists (**Annex 4**). [4,18] If we suspect there is someone, then we should perform a CT scan before lumbar puncture, or delay it until the patient stabilizes, and start antibiotherapy. [21] Both, biochemical and microbiological study have to be done. [4,18,21] While with biochemical study we can guide the diagnosis to bacterial or other types of meningitis; with microbiological study we can identify the causative microorganism. [18] In the box below there is a summary of these studies and its results in IMD.

	Parameters studied & Results
Biochemical study	❖ Appearance: cloudy or pus-like. ❖ Decreased level of glucose respect serum value. ❖ Raised levels of proteins. ❖ Increased white cell count and predominance of polymorphonuclear leucocytes. In early illness it can be normal, but with repeated analyses a turn is observed.
Microbiological study	❖ Direct microscopy observation by Gram technique to detect Gram negative diplococci. ❖ Culture to isolate meningococcus. A negative result does not discard IMD diagnosis, especially if the patient has been treated with antibiotics. ❖ PCR to detect DNA of *N. Meningitidis.* ❖ Fast antigen detection for meningococcus. Is useful when the others are negative.

The need of lumbar puncture in sepsis cases without meningitis is controversial, because in absence of meningitis, lumbar puncture is not helpful in diagnosis process and can lead to delay treatment. [2]

- **PCR:** is a newish technique that identifies DNA from meningococcus in different tissues or fluids. Its advantages respect cultures include: more sensitivity, faster diagnosis and its result is not influenced by prior antibiotic administration.

However, PCR has less specificity than cultures. Nowadays, it is available in most centres. So, if it is possible, PCR should be performed as well as culture to confirm an IMD and identify the responsible strain. Hence, the main reference tests to confirm an IMD case are culture and PCR. [2,20,21]

To conclude, meningococcal isolation in non-usually sterile environments, such as pharyngeal exudate or skin lesions, requires a carefully interpretation. [2]

Skin lesions: meningococcus is not a commensal organism of the skin, so its identification in suggestive skin lesions of IMD can help in the diagnosis. However, the study of skin lesions is not performed regularly, for that reason some studies do not recommend it as a diagnostic method to confirm IMD. [2]

Pharyngeal exudate: in a variable percentage of the population, *N. Meningitidis* could be a commensal microorganism colonizing the nasopharyngeal epithelium without causing any disease. That is why, a positive culture of pharyngeal exudate cannot be considered as indicative of IMD. [2]

Finally, a blood test may also be done in all patients initially. Although it is not possible confirm an IMD case with a blood test, it provides useful information about patient's state and helps to make therapeutically decisions. [4,21]

The most important parameters that must be assessed are: [2,21]

- Blood count: particularly it is important to analyse the leukocyte formula and the neutrophil count. We will usually find leucocytosis and neutrophilia. A normal or diminished white cell count is considered as bad prognosis sign.
- CRP: according to some studies, it has a high negative predictive value and levels under 6 mg/dL at admission nearly discard IMD.
- Procalcitonin: although its role in daily clinical practice has not been stablished yet, it seems this inflammatory marker has similar diagnosis characteristics to CRP. However, further studies are needed to clarify its usefulness.
- Erythrocyte sedimentation rate: an increase of that analytical parameter for >24 hours may indicate an IMD combined with the others.
- Coagulation: an alteration of coagulation tests indicates severity, because it can indicate a DIC process.
- Ionogram: it helps to determine if there are electrolyte imbalances and endocrinologic complications as adrenal insufficiency or inappropriate antidiuretic hormone secretion syndrome.

- ❖ Other biochemical parameters: such as hepatic or renal function. We can assess if there is a multiorgan damage.

11. TREATMENT

Patients with suspicion of meningococcal meningitis or sepsis must receive antibiotherapy as fast as possible, as well as supportive care measures if it is necessary. Before we administrate antibiotics, we should perform cultures and other tests mentioned before. [7]

A topic in discussion is the use of pre-admission antibiotics in suspected cases of meningococcal disease, in order to prevent its potentially fatal consequences. Although this measure could be beneficial, it would also mean we are treating people we do not know if they are really sick. So, unnecessary antibiotics could be given to that patients. Sudarsanam *et al*. [22] made a review with the aim to assess the efficacy of that measure. It concludes that due to lack of evidences it is not possible to support or refute its use. Therefore, further studies are required.

A properly management of IMD includes its treatment at hospital with parenteral antibiotics and supportive care measures if the patient requires it. [2]

Regarding antibiotic therapy, recommended empirical drugs are ceftriaxone or cefotaxime. [2,6,7] Once we have the microbiological results and we know meningococcal sensitivity to penicillin then we can adjust treatment if it is necessary. [2,6]

In the following figure there is the specific treatment according with meningococcal sensitivity to penicillin. [6]

Penicillin sensitive Meningococcus (MIC <0,1 µg/dL)

- Penicillin G 250.000-300.000 U/kg/day
- Allergic patient to penicillin without anaphylactic reaction: Ceftriaxone
- Allergic patient to penicillin with anaphylactic reaction: Chloramphenicol

Meningoccocus with decreased sensitivity to Penicillin (MIC 0,1 - 0,8 µg/dL)

- High dosis of Penicillin G
- Alternative: Cefotaxime

Penicillin resistant Meningococcus (MIC >0,8 µg/dL)

- Cefotaxime, Chloramphenicol or Ceftriaxone and perform a more detailed antibiogram

Figure 2. Treatment for MD according with sensitivity to penicillin. Adapted from [6]

Treatment should be maintained for 7-10 days, although there is controversy on that issue.[2,6,7] Those patients treated with Penicillin or Chloramphenicol must receive also treatment with Ceftriaxone in order to eliminate meningococcus from their nasopharynx and avoid spreading the infection. [6]

About corticosteroids, its use is highly discussed. Several papers have recognised corticosteroids are beneficial in acute bacterial meningitis[2,7,18] reducing hearing loss, neurological sequelae and mortality rates, although those benefits have not been observed in patients with meningococcal disease. However, it seems logical to think these results would be expected in meningococcal disease cases, so they are used routinely.[7]

Molyneux et al. [23] has observed a possible relationship between socioeconomically level and the response to corticosteroids. One explanation for that fact could be those children with low socioeconomic status have a basal secretion of cortisol higher than children with high socioeconomic level. This could reduce the effect of corticosteroids in children with low socioeconomic level. So, the positive effects of corticotherapy could be observed only in high socioeconomically levels. [6]

Finally, in case of MS it is not recommended corticosteroids use unless the patient has a refractory shock to catecholamine treatment.[2]

On the other hand, supportive care measure for MS includes several procedures carried out during the first 6 hours in order to maintain cardiovascular stability, a correct oxygenation level and restore the metabolic balance [2]

In a patient with cardiovascular shock rehydration through intravascular fluids and catecholamine should be started in early stages in order to reduce mortality. [2,5,6]

It is known that an insufficient or delayed treatment is related with an increased mortality. Hence, according with the National Health Ministry guide supportive measures should be done as fast as possible.[2]

The most important supportive care measures are:

- **Intravenous fluids**: they are the first measure to carry out. Given the absence of tests whom indicate the optimal level or volume of fluids to administrate in those patients, we administrate fluidotherapy until we achieve the objectives of resuscitation or until we see signs of volume overload. [2,5,19]

  There is no evidence enough about which fluid (crystalloid or colloid) should be recommended in paediatric patients. However, crystalloid fluids are more cost-effective than colloid fluids.[2]

- **Catecholamine:** When fluids are not enough and several signs and symptoms such as hypotension, delayed capillary fluid, tachycardia or cold extremities are still present after fluidotherapy, this is a fluidotherapy refractory shock. Then, we have to start treatment with vasopressive drugs. [2,5,19]

To conclude, those patients may have a catastrophically and fast evolution to instability state who requires an intensive care. After being stabilized, be admitted in ICU improves the prognosis of that patients, as well as be attended for paediatrician experts. [2]

However, although all that measures the mortality due to septic shock is still today high. [2,5,19]

12. PREVENTIVE MEASURES

Preventive measures include both vaccination and chemoprophylaxis in close contacts of cases. [2,16]

In addition, other effective measures are general recommendations to avoid respiratory transmission such as wash your hands before and after touching a patient, patient isolation,

wear a mask; and inform to the Public Administrations when cases appear in order to put in practice adequate prevention procedures in population at risk. [16]

Chemoprophylaxis

Its main objectives are reducing the transmission of *N. Meningitidis* from sick people or carriers to healthy people and eradicate carriers state in neocolonized who are vulnerable to develop an IMD (those who have been colonized during the last 7 days). [2]

The antibiotics for the chemoprophylaxis are:

Drug	Age Group	Doses	Duration
Rifampicin **Oral administration**	Children <1 month	5 mg/kg every 12 hours	2 days
	Children > 1 month	10 mg/kg every 12 hours	
	Adults	600 mg every 12 hours	
Ceftriaxone **Intramuscular administration**	Children < 15 years	125 mg	Single dose
	Adults	250 mg	
Ciprofloxacin **Oral administration**	Adults* *in children can produce arthropathy	500 mg	Single dose

Figure 3. Chemoprophylaxis for IMD from [2]

Vaccinations

Vaccination is a preventive measure that helps to avoid secondary cases of IMD when it is combined with chemoprophylaxis. [9] Moreover, it has been recognised as the most effective way of prevent bacterial meningitis in children. [18]

About meningococcal vaccines, in our environment we have an effective conjugated vaccine for prevent IMD due to *N. Meningitidis* serogroup C. This vaccine showed its efficacy during epidemic outbreaks and since year 2000 it is included in our routine vaccination schedule. [2,8,10,24]

It also exists tetravalent conjugated vaccines against serogroups A, C, Y and W135 that are recommended for patients who travel to endemic regions for that serogroups or immigrants who are from those regions.

Nowadays, polysaccharide vaccines are not used today in paediatrics and they have been replaced for conjugated vaccines, which are: more effective, can be administrated in children >2 months and produce a fast and durable T-Dependent immune response. Moreover, this type of vaccine can eradicate carriers, helping to control the disease. [9,16,25]

Recently, a new vaccine has been developed for prevent IMD due to meningococcus serogroup B. Several aspects of that vaccine will be the objective of that protocol.

JUSTIFICATION

Invasive Meningococcal Disease is still today an important infectious disease that causes mortality, morbidity and a big social alarm. Despite of scientific advances, its prompt diagnosis and treatment continue supposing a big challenge for physicians, who must act rapidly, due to the quick onset and course of the disease and the possibility of major sequelae. [2,26]

According to current data about IMD epidemiology, we know that, despite IMD has a tendency to decrease, the main serogroup responsible of IMD cases is meningococcus B in several European countries including Spain. [10,14,15]

Moreover, it is known that an active immunisation through vaccines is the best measure for primary prevention of IMD. [26]

For years, big efforts have been made to develop an effective vaccine against meningococcus B. However, developing that vaccine has been really difficult, because capsular structure of meningococcus B acts as a self-antigen. This fact caused that, conventional conjugated vaccines produce lower immune response thus lower antibodies production and, potentially, autoimmune responses. So, instead of conventional vaccines it was necessary a different type of vaccine. [26]

Finally, on January 2013 a new vaccine called 4CmenB (Bexsero) produced by a new technology, known as reverse vaccinology, was approved for prevent IMD due to meningococcus B.

However, because Bexsero is a new vaccine obtained through a newer technology many aspects about this vaccine are unknown and that fact generates controversy in its use. [14,27,28]

On the one hand, what we know about Bexsero is that the vaccine is immunogenic. That means it generates high antibodies titers with bactericidal activity against antigens included into the vaccine. There are also studies that show the vaccine has been effective for controlling epidemic outbreaks in United States and Quebec. [27,29,30] An important aspect about this information is that it has been obtained in teenagers and adults. [30,31] There are no studies carried out in children.

On the other hand, there are many other things we do not know about Bexsero, such as its real effectiveness in IMD prevention, its safety, its interaction with the other routine

vaccines, its coverage of the meningococcus B strains of our country, the period of time during which the person is protected, if the vaccine is capable of erradicate carriers or if it is recommended in high risk groups of population. [14,27,31]

Hence, given the lack of information about Bexsero the Spanish Vaccinology Association and the Health Ministry [14] as well as work groups for Bexsero's use in special situations [28] have elaborated several documents and recommendations about the use of the vaccine. Together, those entities do not recommend a systematic use of Bexsero.

On the contrary, pediatricians and the Vaccine Advisory Committee of the Spanish Pediatrics Association [15] advise a routinary use of Bexsero and encourage parents to vaccinate children. In fact, they are asking for introduce Bexsero into the routine vaccination schedule.

Furthermore, other European countries such as Italy [11], France [32] have found different results when they asses the effects of Bexsero in its population.

Recently, United Kingdom has introduced Bexsero as a routine vaccine and, since 2015, they are collecting data about its effectiveness in their population.

In conclusion, given the existing controversies about Bexsero use and the lack of strong evidences about its real efficacy in IMD prevention; further studies are required to really know the effects of that vaccine.

For that reason, the aim of this protocole is designing a study that assesses, mainly, the effectiveness of Bexsero for prevent IMD in children aged among 3 moths and 5 years old, since those are the most affected for this disease and, in addition, there are no studies performed in that age group. Moreover, it will also provide information about its adverse reaction profile.

HYPOTHESIS

PRIMARY

Children under 5 years old who have been vaccinated with Bexsero have lower incidence of invasive meningococcal disease in comparison with unvaccinated children.

SECONDARY

Children under 5 years old vaccinated with Bexsero as well as routinary vaccines show a higher proportion of adverse reactions than those who just receive routinary vaccinations.

OBJECTIVES

MAIN OBJECTIVE

- To asses the effectiveness of Bexsero in prevention of invasive meningococcal disease in children aged among 3 months and 5 years old.

SECONDARY OBJECTIVES

- To compare the occurrence of adverse reactions among children vaccinated with routinary vaccines and Bexsero versus children vaccinated with routinary vaccines.

METHODOLOGY

STUDY DESIGN

This is an observational prospective cohort study. It will have two groups:

- Cohort 1: it will include children vaccinated with Bexsero.
- Cohort 2: it will include children non vaccinated with Bexsero.

The follow-up period will last 5 years, and during that time we will observe how many cases of IMD occur in each cohort to stablish the effectiveness of Bexsero vaccination.

Concurrently, we will collect information about adverse reactions due to vaccination registered in each cohort, in order to compare it.

STUDY POPULATION

The target population of the study are children (boys and girls) aged among 3 months to 5 years old, who are attending to Public Health System and whose data about visits and vaccinations are registered into the SIDIAP.

Inclusion criteria

- Children aged among 3 months and 5 years old.
- Health Centres that participate in the study register patient's information into SIDIAP database.

Exclusion criteria

- Children that are not receiving regularly vaccines.
- Previous antecedent of meningococcal meningitis or sepsis.
- Children with one of the following pathologies: *

  Persistent complement deficiencies.

  Primary or secondary immunodeficiencies.

  Anatomical or functional asplenia.

*The reason why it is necessary to exclude those children is because they have different vaccination regimens from those of the general population.

SAMPLE PROTCOL

Sample selection

The sample will be selected, taking into account the mentioned inclusion and exclusion criteria, from registers contained into SIDIAP database. A non-probabilistic consecutive sampling method is employed in this study.

All children that accomplish previously mentioned criteria will be included.
The enrolment period starts on June 2017 and finishes on June 2018, lasting 1 year.

The desired follow- up for each participant should be 5 years, because this is the period where higher incidence rates occur among paediatric population.

Sample size

The application "GRANMO" has been used to calculate the sample size required. The ARCSINUS approximation has been used.

Accepting an alpha risk of 0.05 and a beta risk of 0.10 in a bilateral contrast, we need 14.108 vaccinated children (cohort 1) and 70.540 unvaccinated children (cohort 2) to detect statistically significant differences, considering an efficacy of Bexsero greater than or equal to 70%.

The incidence of IMD in unvaccinated children has been obtained from official data published by "Red Nacional de Vigilancia epidemiológica (RENAVE)" and is 16 cases /100.000 hab per year.

Dropout rate is estimated as 5%.

STUDY VARIABLES

- **Independent variable**: In this study, independent variable is defined as to have been or not to have been vaccinated with Bexsero.

  To classify a child as vaccinated, he must have finished the vaccination regimen according to his age as we can see in the table below adapted from the technical file of Bexsero. Booster doses are not required to consider a child as correctly vaccinated.

Age group	Primary immunisation	Dose interval	Booster dose
From 2 months to 5 months	3 doses of 0.5 ml each one, starting the first dose at 2 months or later.	At least 1 month.	1 dose between 12 and 15 months. Never after 24 months.
From 6 months to 11 months	2 doses of 0.5 ml each one.	At least 2 months.	1 dose during the second year of life with a minimum dose interval of 2 months since the primary immunisation.
From 11 months to 23 months	2 doses of 0.5 ml each one.	At least 2 months.	1 dose with a dose interval from 12 to 23 months since the

			primary immunisation.
From 2 years to 10 years	2 doses of 0.5 ml each one.	At least 2 months.	Not established.
11 years or more	2 doses of 0.5 ml each one.	At least 1 month.	Not established.

Vaccination's state will be collected checking the code corresponding to Bexsero: **P00157**.

- **Outcome variable:** In that case, outcome variable for the primary objective is the number of cases of IMD. As it has been said in the introduction we mainly consider IMD as:

  Meningitis: it is defined as an inflammatory process of the leptomeningeal membranes who overcoat the CNS.

  Information about diagnosis of meningococcal meningitis is codified in hospital registers as **036.0.**

  Sepsis: it is defined by the presence of systemic inflammatory response syndrome due to an infection (suspected or confirmed). That syndrome is characterised by the presence of 2 of the following:

  - Axillary temperature >38ºC or <35,5ºC. *
  - Tachycardia: cardiac frequency >2 Standard Deviations according to the age of the patient without medication or external or painful stimuli.
  - Tachypnea: respiratory frequency > 2 Standard Deviations according to the age of the patient.
  - White cell count elevated or diminished for the age of the patient or >10% of immature neutrophils. *

  * Criteria must be present.

  Information about diagnosis of sepsis is codified in hospital registers as **036.2** (meningococcal sepsis) and **036.3** (Sd. Waterhouse-Friedrichsen).

  Finally, the outcome variable for the secondary objective are adverse reactions due to vaccination.

Adverse reaction: it is defined as a harmful and undesirable reaction which is produced with normal doses used in humans for prevent, diagnose or treat a disease.

We consider adverse reactions all reactions, local or systemic, caused by vaccinations:

Local adverse reaction: local pain, cutaneous erythema, swelling.

Systemic adverse reaction: Fever >38ºC, irritability, bad general condition.

Information about adverse reactions is codified as **T66.**

- **Covariables**: it is important to control several factors that may interfere with the possibility of a child receives or not the vaccine.

  Those variables will be:

  Sex: Male or Female.

  Age: measured in months and years.

  Ethnicity: Caucasian, Asian, Afro-American and others.

  Socioeconomical status: according with MEDEA index included into SIDIAP and expressed in percentiles.

DATA COLLECTION

Data will be obtained from SIDIAP (Sistema d'Informació pel Desenvolupament de la Investigació en l'Atenció Primària). That database integrates information from several sources, but mainly from e-CAP, which collects information belonging to Primary Attention, and CMBD (Conjunt Mínim Bàsic de Dades), which contains information from Hospital registers like admission diagnosis, patient's evolution, complications, reasons of discharge, etc. However, there are other information sources into SIDIAP database.

Those data represent nearly an 80% of population in Catalunya.

Through SIDIAP we can access to demographical information such as sex, age, race, socioeconomical status, etc; as well as information about health problems, results of complementary tests and therapeutically procedures or vaccinations received by the patient.

VARIABLE DESCRIPTION AND STATISTICAL ANALYSIS

UNIVARIANT ANALYSIS

- Independent variable: it is a dichotomous qualitative variable. It is registered as: Vaccinated or Unvaccinated and described with percentages.
- Dependent variables:
  - Number of cases of invasive meningococcal disease: it is a discrete quantitative variable. It is defined by mean and standard deviation if it is normally distributed or by median and quartiles in case of non-normal distribution. It will be expressed a confidence interval of 95%.
  - Adverse reactions registered: it is a dichotomous qualitative variable. It is registered as presence of adverse reaction associated with vaccination (Yes or No). It will be described by percentages.
- Covariables:
  - Sex: it is a dichotomous qualitative variable, described by percentages.
  - Age: it is a discrete quantitative variable, defined by mean and standard deviation if it is normally distributed or by median and quartiles in case of non-normal distribution. It will be expressed a confidence interval of 95%.
  - Ethnicity: it is a categorical qualitative variable, described by percentages.
  - Socioeconomical status: it is a discrete quantitative variable and it will be described by mean and standard deviation if it is normally distributed or by median and quartiles in case of non-normal distribution. It will be expressed a confidence interval of 95%.

BIVARIANT ANALYSIS

To compare the independent variable, which is categorical qualitative, with the main dependent variable, which is discrete quantitative, we will use the Mann-Withney test.

To compare the independent variable with the secondary dependent variable, which are both categorical qualitative we will use the Chi ^{2} test.

To compare qualitative variables between them we will use Chi^2 test, and to compare quantitative variables between them the Pearson rank or Spearman rank, depending if they are normally distributed or not.

MULTIVARIANT ANALYSIS

It will be used a Cox model adjusted for Propensity Score punctuation, for confounding variables.

ETHICAL AND LEGAL CONSIDERATIONS

The present protocol will be presented for its approval to the Comité d'Ètica i Investigació Clínica (CEIC) de l'Institut d'Investigació i Recerca en Atenció Primària Jordi Gol.

Moreover, we will present that protocol to the Agencia Española del Medicamento y Producto Sanitario (AEMPS) since this is a post-authorisation observational study and it has to be classified.

Once we have obtained the Ethics Commitee's approval and the AEMPS's classification, we present the protocol to the Departament de Salut de Catalunya- Subdirecció General de Recerca i Innovació en Salut, since we are using a vaccine which is a drug.

Finally, in a voluntary way, we will register that protocol to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) in order to avoid a possible publication bias.

The project will guarantee that the following considerations and legislations are respected:

- World Medical Association -Declaration of Helsinki: Ethical Principles for Medical Reasearch Involving Human Subjects from 1964.
- Spanish Law: "*Ley 14/2007 de Investigación Biomédica"*
- *Real Decreto 1090/2015- Regulación de los Ensayos Clínicos con medicamentos, Comités de Ética de Investigación con medicamentos y el Registro Español de Estudios Clínicos.*
- *Orden SAS/3470 de 2009- Directrices sobre Estudios Post- Autorización de Tipo Observacional para Medicamentos de Uso Humano.*

Because we are using a preexisting database as SIDIAP where all information is anonymised and codified it is no necessary ask for Informed Consent, according with current legislation:

- *Ley Orgánica 41 de 2002- Autonomia del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.*
- *Ley Orgánica 15 de 1999- Protección de Datos de Carácter Personal.*

The investigators have no conflict of interests.

STRENGTHS AND LIMITATIONS

As any other study, certain limitations exist. Those limitations can be related with the study design, its associated biases and with the sample's obtention.

STUDY DESIGN

Although Clinical Trial is the best design for assess the effectiveness of a preventive measure, that design would entail several difficulties, which would seriously affect the results obtained and its validity.

The main reason to not perform a Clinical Trial is that given the low incidence of IMD at current moment, it would be necessary to enrol a lot of participants in the study and also a long follow-up period to obtain IMD cases and see if the vaccine is effective or not in its prevention.

Therefore, to carry out a Clinical Trial a big inversion of time and resources will be needed, so it would not be feasible right now.

To solve all that issues it has been choosen a cohort study and a data source as SIDIAP. That data source allows the obtention of sufficient participants, and the design allows its follow-up during an adequate period of time, making feasible the study even the current epidemiological situation.

BIASES

Observational studies have an important limitation, because we cannot randomly assign participants to one group or another.

That fact causes that differences observed may be due to the existence of confounding variables.

For that reason, in this study it is very important controlling that confounding variables. Hence, they are collected during data collection phase and controlled with a multivariant anlysis.

The analysis we will perform will be adjusted with the Propensity Score (PS).

PS is a useful tool that helps to know if we are comparing two groups that are similar between them except for the independent variable we are studying.

So, we establish *a priori* which variables can be confounding and, according with PS punctuation, we will know if two groups are homogeneus and the results that we are observing are due to the measure we are assessing.

SAMPLE

The big sample size required to carry out the study could be a limitation, however because we obtain information through SIDIAP database, which includes a high part of population in Catalunya, we can easily access to all information required as well as obtain a sufficient number of participants in the study.

In fact, using a big sample provides a high external validity to the results since the sample we are studying is highly representative from target population.

WORK PLAN

In this section we are going to describe the phases of the study as well as which activities will include, who is going to carry out every phase and how long is going to take each one.

The study will last 7 years and 4 months and it will be structured in 4 phases.

PHASE 1- Coordination & Development of the protocol (6 months)

- Activity 1: Meeting to define who is going to participate in the investigation and assigning functions to every member of the research team. All members participate. (M1)
- Activity 2: Defining an Hypothesis, Objectives and Variables for its collection from SIDIAP database. All members participate. (M1-M2)
- Activity 3: Bibliography research. Three members of the research team. (M1- M2)
- Activity 4: Pilot test of data extraction, problems detection and correction. Two members of the research team. (M3)
- Activity 5: Elaboration of final protocol. All members participate. (M3-M4)
- Activity 6: Sending the protocol to the Ethics Commitee and to AEMPS for its aproval and classification. Main investigator & another member of the research team. (M4-M6)
- Activity 7: Register the protocol into ENCePP. Main investigator. (M6)
- Activity 8: Design a database for the study. One member of the research team. (M3-M6)

PHASE 2- Participants recruitment & Data collection (6 years)

- Activity 9: Participants recruitment will last 1 year. (M6-M18)
- Activity 10: Follow- up for every subject included in the study for 5 years. (M6-M78)
- Activity 11: Data collection. Information regarding variables and covariables for the study will be collected and introduced in our study database. Information will be depurated and reviewed before being introduced into our database. All members participate. (M6-M78)

PHASE 3- Statistical analysis & interpretation of the results (5 months)

- Activity 12: Data obtained will be analyzed by statistician. One member of the research team. (M78-M80)
- Activity 13: Investigators will discuss the results obtained, after their statistical analysis. All members participate. (M80-M82)

PHASE 4- Final report elaboration & Publication of the results (5 months)

- Activity 14: Final report writting. Main investigator. (M83-M85)
- Activity 15: Final report dissemination: Submitt the results to the principal medical journals to be published. Main investigator. (M85-M87)

STUDY CHRONOGRAM

	2017	2018	2019	2020	2021	2022	2023	2024
PHASE 1- Coordination & Development of the protocol								
Act 1- Coordination meeting								
Act 2- Hypothesis, Objectives & Variables								
Act 3- Bibliography research								
Act 4- Pilot test								
Act 5- Final protocol elaboration								
Act 6- Protocol approval								
Act 7- Protocol register								
Act 8- Database design								
PHASE 2- Participants recruitment & Data collection								
Act 9- Participants recruitment								
Act 10 – Follow- up								
Act 11 – Data Collection								
PHASE 3- Statistical analysis & interpretation of the results								
Act 12- Statistical analysis								
Act 13- Discussion								
PHASE 4- Final report elaboration & Publication of the results								
Act 14- Final report elaboration								
Act 15- Publication of the results								

BUDGET

This study is observational and certain aspects of daily practice are not modified, such as indications or recommendations for vaccination with Bexsero given by paediatricians and the decision of vaccinate or not vaccinate made by parents, Bexsero's administration place, number of doses, children's visits schedule or Primary or Hospitalary attention in IMD cases (complementary tests performed, treatments administrated).

For that reasons, the cost of Bexsero is not included in the budget. Moreover, paediatricians and nurses who are going to administrate Bexsero and make the visits to the participants, making the recruitment and follow-up will not receive a special compensation.

To make the statistical analysis, a qualified statistician will be hired. He will be payed 25€/hour with an estimated time for this work of 120 hours, so the total amount will be 3.000€.

To create a specific database for our project, a data manager will be hired. Create our own database is an important point, because into SIDIAP there is a lot of information that is not necessary to answer our study question, so data must be debugged and transformed in order to be analysed. In addition, it is necessary to guarantee that data are correctly anonymised in order to not infringe ethical principles. The cost of create the database, extract data from SIDIAP and introduce it into our database, debugger it, encrypt it and maintaining the database for 7 years is estimated of 4.300 €/ year, so the total amount will be 30.100 €.

To discuss the results obtained at the end of the study, the meeting will have an estimated cost of 400 €.

Publication of the results in Open Access will suppose a cost of 1.500 €.

To summarise the estimated cost of the project, the following box has been made.

PERSONNEL COSTS		
Statistician	25 €/hour x 120 hours	3.000 €
Data manager Estimated cost of create our own database, import information from SIDIAP, debugger data, encrypt it and maintaining the database for 7 years.	4.300 € / year x 7 years	30.100 €
	SUBTOTAL	33.100 €
MEETING COSTS		
Meeting for results discussion		400 €
	SUBTOTAL	400 €
PUBLICATION COSTS		
Publication of the results in Open Access		1.500 €
	SUBTOTAL	1.500 €
	TOTAL AMOUNT:	**35.000 €**

FEASIBILITY

With an accumulate incidence rate of 16 cases /100.000 hab per year [14] and a source of data as big as SIDIAP obtaining data from Catalunya and not just from one province, one year should be enough to achieve the sample required or even more participants.

According with the information needed, no modifications have to be done in the e-CAP or CMBD to obtain data about variables, so with current tools it is perfectly possible to start with this study.

In conclusion, all necessary means are available and time periods to achieve the objectives of the study are affordable, so the present protocol is feasible right now.

IMPACT TO THE NATIONAL HEALTH SYSTEM

This study will have a big impact on our National Health System for several reasons.

First, the use of Bexsero is a current topic in discussion since this vaccine is relatively new and it exist a high controversy among paediatricians about if it has to be massively administrated or not. Moreover, there are no strong evidences to support for or against opinions regarding its use.

Therefore, it is important to know if Bexsero is really effective for prevent a severe, life threatening disease which also causes major sequelae in children as the invasive meningococcal disease. In fact, if Bexsero was effective it could be included into the regularly vaccination schedule in order to benefit the entire population.

On the contrary, if the vaccine is not useful for IMD prevention it would be convenient know it in order to avoid using it in healthy children.

Hence, regardless if the hypothesis of the study is true or not the results of the study could change the daily practice in Paediatrics.

Secondary, if our results point that there is an association among being vaccinated with Bexsero and have more adverse reactions, that fact would change current recommendations about that vaccine. Even more, knowing if this association exists could be very useful in order to start other research projects about this topic and stablish a possible causal relationship.

BIBLIOGRAPHY

1. Crum-Cianflone N, Sullivan E. Meningococcal Vaccinations. Infect Dis Ther [Internet]. 2016 [cited 2016 Nov 5];5(2):89–112. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27086142

2. Ministerio de Sanidad. Guía de Práctica Clínica sobre el Manejo de la Enfermedad Meningocócica Invasiva. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2013.

3. Gil Á, Barranco D, Batalla J, Bayas JM, Campins M, Gorrotxategi Gorrotxategi P, et al. Prevención de la enfermedad meningocócica por el serogrupo B mediante una vacuna de cuatro componentes. An Pediatr. 2014;16(62):259.e1-259.e23.

4. Tellez Gonzalez C, Reyes Dominguez S. Meningitis Bacteriana Aguda. Sociedad Española de Cuidados Intensivos Pediátricos (SECIP); 2010.

5. Alonso Salas M, de Carlos Vicente JC, Gil Antón J, Pinto Fuentes I, Quintilla Martinez J, Sánchez Díaz J. Documento de consenso SECIP-SEUP sobre manejo de sepsis grave y Shock séptico en pediatría [Internet]. Sociedad Española de Cuidados Intensivos Pediátricos (SECIP); 2009 [cited 2016 Nov 15]. p. 76. Available from: http://www.seup.org/pdf_public/pub/consenso_sepsis_shock.pdf

6. Colino Gil ME, Paez JP, Chamizo López FJ. Diagnóstico y tratamiento precoz de la enfermedad meningocócica. An Pediatr Contin. 2011;9(6):375–82.

7. Strelow VL, Vidal JE. Invasive meningococcal disease. Arq Neuropsiquiatr. 2013;71(9 B):653–8.

8. Martínez AI, Domínguez Á, Oviedo M, Minguell S, Jansà JM, Codina G, et al. Epidemiología de la enfermedad meningocócica en Cataluña antes y después de la vacunación frente al serogrupo C. Rev Esp Salud Publica. 2009;83(5):725–35.

9. Red de Vigilancia epidemilógica. Protocolo de Actuación frente a Enfermedad meningocócica. Madrid: Servicio Madrileño de Salud; 2011. p. 1–17.

10. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine. 2009;27(Suppl. 2):B51–63.

11. Gasparini R, Landa P, Amicizia D, Icardi G, Ricciardi W, de Waure C, et al. Vaccinating Italian infants with a new multicomponent vaccine (Bexsero) against meningococcal B disease: A cost-effectiveness analysis. Hum Vaccines Immunother. 2016;12(8):2148–61.

12. Vázquez JA. Situación actual de la epidemiologia de la enfermedad meningocócica. Sociedad Española de Enfermedades Infecciosas y Microbiologia Clínica (SEIMC); p. 1–8.

13. Stanton MC, Taylor-Robinson D, Harris D, Paize F, Makwana N, Hackett SJ, et al. Meningococcal disease in children in Merseyside, england: A 31 year descriptive study. PLoS One. 2011;6(10):1–7.

14. Asociación Española de Pediatria, Asociación Española de Vacunología. Vacuna frente a la enfermedad meningocócica invasora por serogrupo B. Información para profesionales sanitarios [Internet]. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2016 [cited 2016 Nov 20]. p. 12. Available from: www.msssi.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/doc

s/VacunacionMeningococo_ProfSanitarios.pdf

15. Moreno-Pérez D, Álvarez García FJ, Arístegui Fernández J, Cilleruelo Ortega MJ, Corretger Rauet JM, García Sánchez N, et al. Vacunación frente al meningococo B. Posicionamiento del Comité Asesor de Vacunas de la Asociación Española de Pediatria. An Pediatr. 2015;82(3):198.e1-198.e9.

16. Centro Nacional de Epidemiologia, Instituto de Salud Carlos III. Protocolos de las enfermedades de declaración obligatoria. Madrid: Red Nacional de Vigilancia Epidemiológica; 2013.

17. Dowson A. Meningococcal disease in children and teenagers. Nurs Times [Internet]. 2014 [cited 2016 Nov 26];110(11):12–5. Available from: http://search.proquest.com/docview/1509080185?accountid=11648

18. Sáez-Llorens X, McCracken GH. Bacterial meningitis in children. Lancet. 2003;361(9375):2139–48.

19. Payo Pérez R, Serrano Ayestarán O. Protocolos de Infeccioso. Manejo inicial de la sepsis- shock séptico pediátrico. Bol Pediatr. 2006;46(Suppl. 1):107–12.

20. European Centre for Disease Prevention and Control. Public health management of sporadic cases of invasive meningococcal disease and their contacts. 2010.

21. Artigao FB, López RV, Martín FC. Meningitis bacteriana. Protocolos diagnóstico-terapéuticos de la AEP: Infectología pediátrica. Madrid; 2011. p. 47–57.

22. Td S, Rupali P, Tharyan P, Oc A, Thomas K. Pre-admission antibiotics for suspected cases of meningococcal disease (Review). Cochrane Library; 2013.

23. Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: A randomised controlled trial. Lancet. 2002;360:211–8.

24. Morales D, Moreno L, Herranz M, Bernaola E. Enfermedad meningocócica invasiva en Navarra en la era de la vacuna conjugada antimeningocócica C. An Pediatr. 2016;1–7.

25. Pineda Solas V. Vacunas conjugadas. Rev Pediatr Atención Primaria. 2005;7(Suppl. 4):S65–74.

26. Kuhdari P, Stefanati A, Lupi S, Valente N, Gabutti G. Meningococcal B vaccination: real-world experience and future perspectives. Pathog Glob Health [Internet]. 2016;110:148–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27309042

27. Sánchez NG, Hernández Merino A. Vacunas : novedades y controversias. AEPap Curso Actual en Pediatr. 2015;187–98.

28. Limia Sánchez A, Sierra Moros M, Cano Portero R, Salmerón Garcia F, Vázquez Moreno J, Mayoral Cortés J, et al. Recomendaciones de utilización de la vacuna frente a enfermedad meningicócica por serogrupo B. Ministerio de Sanidad, Servicios Sociales e Igualdad; 2014.

29. Harrison LH. Vaccines for Prevention of Group B Meningococcal Disease: Not Your Father's Vaccines. Vaccine [Internet]. 2015;33:D32–8. Available from: http://dx.doi.org/10.1016/j.vaccine.2015.05.101

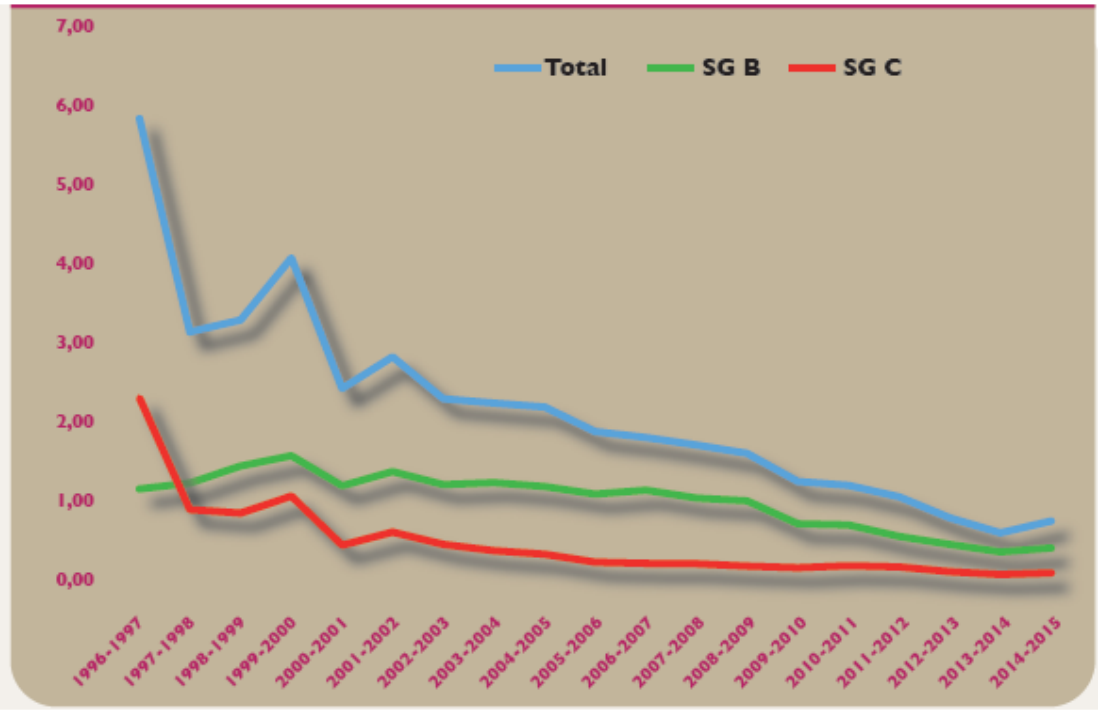
30. Llerena Santa Cruz E, Buñuel Álvarez J. La nueva vacuna multicomponente para el meningococo serogrupo B en adolescentes tiene una buena inmunogenicidad a

corto plazo. Evid en Pediatr. 2012;8:73.

31. Juanes De Toledo B, Ruiz-canela Cáceres J. Un paso más para la vacuna frente al meningococo B dentro del calendario vacunal. Evid en Pediatr. 2012;8:37.

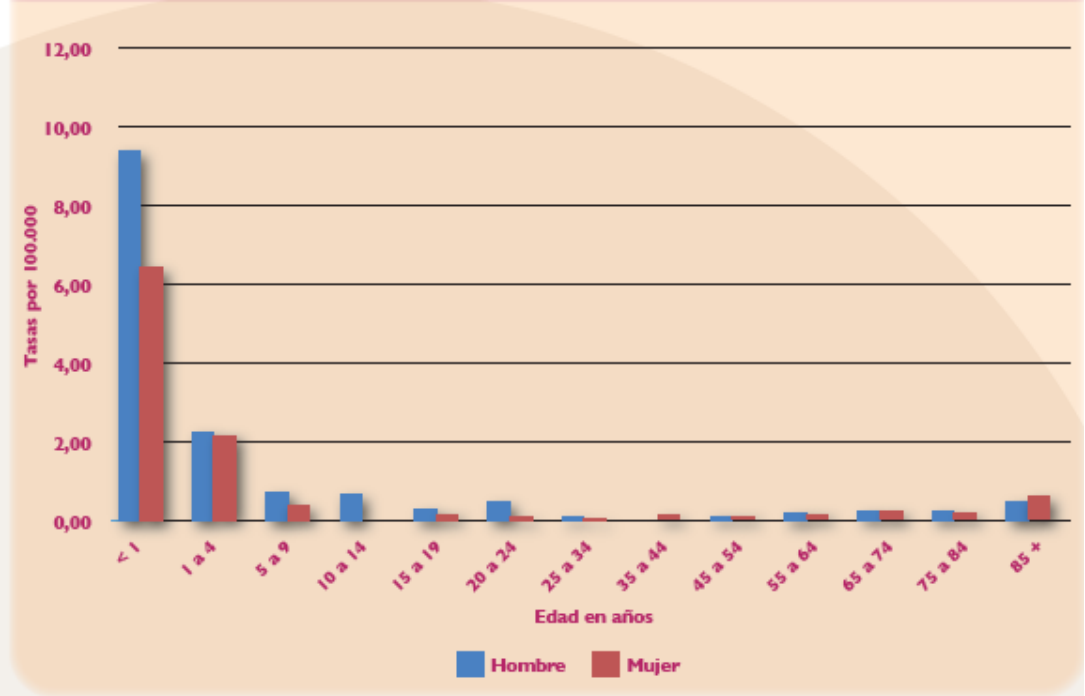
32. Lecocq H, Parent du Châtelet I, Taha MK, Lévy-Bruhl D, Dervaux B. Epidemiological impact and cost-effectiveness of introducing vaccination against serogroup B meningococcal disease in France. Vaccine [Internet]. 2016;34(19):2240–50. Available from: http://dx.doi.org/10.1016/j.vaccine.2016.03.020

ANNEX 1: EVOLUTION OF INCIDENCE RATES OF MENINGOCOCCAL DISEASE



From: Asociación Española de Pediatria, Asociación Española de Vacunologia. Vacuna frente a la enfermedad meningocócica invasora por serogrupo B. Información para profesionales sanitarios. Madrid. Ministerio de Sanidad, Servicios Sociales e Igualdad. 2016.

ANNEX 2: INCIDENCE RATES OF IMD DUE TO SEROGROUP B



From: Asociación Española de Pediatria, Asociación Española de Vacunologia. Vacuna frente a la enfermedad meningocócica invasora por serogrupo B. Información para profesionales sanitarios. Madrid. Ministerio de Sanidad, Servicios Sociales e Igualdad. 2016.

ANNEX 3: Epidemiology of IMD in European Countries in 2011.

Tabla 1 Epidemiología de la enfermedad meningocócica invasora (total y por serogrupo B) en la Unión Europea en el año 2011[7,9]

	Casos totales de EMI confirmados en 2011	Casos de EMI por 100.000 personas/año	Casos totales de EMI por MenB en 2011	Casos de EMI por MenB por 100.000 personas/año
Alemania	370	0,45	219	0,3
Austria	49	0,58	15	0,2
Bélgica	111	–	83	0,8
Chequia	63	0,60	34	0,3
Dinamarca	72	1,30	27	0,5
Eslovaquia	21	0,39	11	0,2
Eslovenia	13	0,63	9	0,4
Estonia	7	0,52	5	0,4
España	**431**	**0,93**	**304**	**0,7**
Finlandia	34	0,63	19	0,4
Francia	563	0,87	395	0,6
Grecia	52	0,46	43	0,4
Holanda	106	0,64	66	0,4
Hungría	67	0,68	28	0,3
Irlanda	89	1,95	84	1,9
Italia	152	0,25	75	0,1
Letonia	2	1,38	1	0,09
Lituania	42	0,10	28	0,9
Luxemburgo	2	0,39	–	–
Malta	6	1,44	2	0,5
Noruega	37	0,75	10	0,2
Reino Unido	1036	1,67	837	1,3
Polonia	282	0,73	152	0,4
Portugal	56	0,54	49	0,3
Rumania	68	0,32	29	0,1
Suecia	68	0,72	15	0,2
Total	3776	0,75	2551	0,5

ECDC: European Centre for Disease Prevention and Control; EMI: enfermedad meningocócica invasora; MenB: meningococo serogrupo B.

Figure from: Moreno-Pérez D, Álvarez García FJ, Arístegui Fernández J, Cilleruelo Ortega MJ, Corretger Rauet JM, García Sánchez N, et al. Vacunación frente al meningococo B. Posicionamiento del Comité Asesor de Vacunas de la Asociación Española de Pediatria. An Pediatr. 2015;82(3):198.e1-198.e9.

ANNEX 4: LUMBAR PUNCTURE CONTRAINDICATIONS

CONTRAINDICACIONES DE PUNCIÓN LUMBAR
• Inestabilidad cardiorespiratoria. • Diátesis hemorrágica: CID, trombocitopenia con plaquetas < 50 000 o un INR >1,4. • Aumento de la presión intracraneal detectado por coma, pupilas anormales, postura, parálisis del III o VI PC, papiledema, bradicardia, hipertensión o alteraciones del patrón respiratorio. • Afectación cutánea de la zona donde se practica la punción lumbar.

Figure from: Tellez Gonzalez C, Reyes Dominguez S. Meningitis Bacteriana Aguda. Sociedad Española de Cuidados Intensivos Pediátricos (SECIP); 2010.