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A Hib vaccine battle with Haemophilus influenzae

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Abstract. With nearly 386,000 deaths caused by Haemophilus influenzae reported by WHO, Haemophilus influenzae is one of the worst killers of children under the age of five. Nowadays, there are places still prone to invasive Hib infections, and numerous areas are still susceptible to Hib-related illnesses. Haemophilus influenza is a bacterium plaguing many families, particularly those with young children. However, antibiotic resistance is increasing. The Hib vaccine may be another solution. The prevalence of Hib infection has dropped significantly after the launch of Hib immunization. The Hib combination vaccination, however, does not protect against all bacterial types. Consequently, certain people may benefit from receiving medical therapy. However, at present, people's understanding of Hib vaccine in many areas is still limited. This study present a thorough and critical evaluation of the most recent understanding of H.influenzae and the medication: Hib vaccine. The focus of this review is to provide an overview of current research on Haemophilus influenzae and also covers how the vaccine works and its advantages and disadvantages.

Keywords: Haemophilus Influenzae, Hib Vaccine, Hib Infections.

1. Introduction

People have recently been monitoring the current Haemophilus influenza (H.influenza) epidemic from all across the world. Nowadays, it has been shown that some communities are still prone to invasive Hib infections, and numerous areas are still susceptible to Hib-related illnesses [1]. In a year, approximately 3 million severe cases related to Haemophilus influenzae. In addition, the mortality is nearly 386,000 reported by The World Health Organization (WHO). It is one of the most horrible killers of those young children under five. Therefore, people need a complete comprehension of the pathophysiology of the various strains of H. influenza and how to avoid and cure them. Up to 80% of children and 20–30% of adults suffer from H.influenza, a Gram-negative coccobacillus lodged in their nasopharynx and throat [2]. H. influenza, however, is divided into six serotypes(a~f). Among them, one is Type B. Therefore, to be more precise, this review focuses mainly on the concept related to type b H. influenza. H. Influenza Type B does not cause influenza. In contrast, H. influenza B, an invasive bacterium, and symptoms after infection depend on the part of the body affected. One is Pneumonia, followed by Meningitis, epiglottitis, cellulitis, septicemic arthritis, and even abscesses and bacteremia [3].

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Several therapeutic methods recommend to cure this disease. Like, as oral cephalosporins or other macrolides, amoxicillin/clavulanate, and omadacycline. Nevertheless, antibiotic resistance lets some of the drugs not work. Fortunately, scientists from the United States successfully published the Hib vaccine, suitable for children in 1987 and babies in 1990. The incident rate of Hib infections has dropped substantially since the arrival of the vaccination. In addition, since 1991, the percentage of terrible Hib illnesses has fallen by more than 99% as several countries approve this technology [4].

Although the safety and efficacy of the Hib vaccine are the top, China is the only country that does not approve of the Hib vaccine because of its high price. To be more specific, children from poor distinct still cannot assess the Hib vaccine. Interestingly, H. influenza incidence and prevalence were higher among Alaska Native children despite Hib vaccination (Incidence: 5.4 per 100 000). To fulfill the Sustainable Development Goals for child survival by 2030 and to speed up the eradication of Hib illness globally, the Hib vaccination should be available and approved in NIP or high-burden areas. Overall, this review focuses on providing an overview of the current H.influenza research and also covers the content of how this vaccine works and its pros and cons. In addition, this review paper will cover seven parts. Pathology, infected population, post infection symptom, therapeutic method, mechanism of hib vaccine, its advantages and side effects after injection, and end with the future challenge-solving part.

2. The characterization of Haemophilus influenza

Haemophilus influenza is the generic name. More precisely, several illnesses were brought on by the bacterium Haemophilus influenza. Types of H. influenza were divided into encapsulated and non-encapsulated (NTHi) groups. The most common encapsulated variety: variety B, is what causes unbelievable infections like meningitis, which affects the endothelium of the brain and spinal cord, as well as pneumonia, which is an infection of the lower respiratory tract [5]. However, for the non-encapsulated group: non-typeable H. influenza (NTHi) plays a majority effect on those patients who have already been vaccinated, especially otitis media, sinusitis, and pneumonia.

The following people are at risk of suffering the Hib disease: Children at the daycare center, American Indians, and patients with immune deficiency. Children having less CPS-specific antibody is the reason for those children being susceptible to Hib disease, as shown by the journal [6].

An infection of the sacs that surround the brain and spinal cord is known as meningitis. The symptoms in children are fever, irritability, loud crying, seizures, loss of appetite, and unusual fatigue. However, for teenagers or adults, they are fever, sensitivity to light, headaches, tiredness, irritability and a rash will develop. Epiglottitis is an inflammation and swelling of the epiglottis. The symptoms in children are fever, sore throat, difficult and painful swelling, drooling, acting anxious and irritable. However, for adults, they are fever, sore throat, a muffled or hoarse voice, difficulty breathing and swallowing. Sepsis is a life-threatening medical emergency. The symptoms in children are loss of appetite, difficulty breathing and waking up from sleep. However, for adults, they are confusion, slurred speech, shortness of breath, and fast breathing.

3. The pathology of Haemophilus influenza

H. influenza infection occurs in the nasopharynx and is spread through direct close contact or inhalation of respiratory secretions from infected individuals. Once the germ has attached to the mucosal outer face of the respiratory tract, it will begin replicating. People with chronic respiratory diseases will be more susceptible to infection because the immune response in the upper respiratory tract is weaker than that of the lower respiratory tract. Once Haemophilus influenza has adhered to a host, it may enter respiratory cells and macrophages, the immune cells that absorb and eliminate foreign infective invaders. While infected, Haemophilus influenza escapes the immune system's attack, adheres to the host tissues, and eventually invades cells [3].

3.1. In the escaping process

A Capsular polysaccharide (CPS), a jelly-like substance composed of sugars, is shielded on the H.influenza. This substance helps bacteria evade the host antibody. After that, bacteria successfully

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escape the engulfment and digestion by macrophages since those macrophages will target antibody-bound bacteria primarily. Although, the immune system (T cells and B cells) tries its best to orient the direction of bacteria. H. influenza bacteria has a protective membrane called the lipooligosaccharide (LOS) (Figure 1) a short chain of sugars. These membrane layers change the appearance of the bacteria to imitate the surrounding. This substance helps bacteria evade the immune cells.

3.2. In the sticking process

Adhesins (Figure 1), surface proteins, behave like bacterial glue by firmly attaching to receptors on the outermost layers of the host cell. Because of them, the process of colonizing becomes easier to carry on. Once the bacteria spread in the bloodstream to distant sites, an inflammation process will occur.

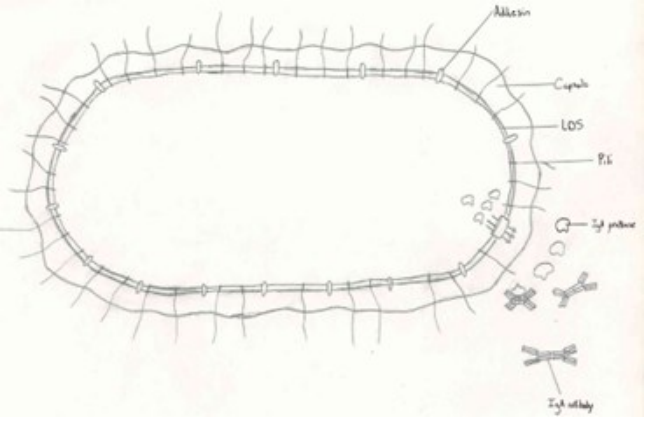

Figure 1. Potential drivers of virulence related to Haemophilus influenzae [7].

4. The treatment of Haemophilus influenza infection

4.1. Take antibiotic

Cefotaxime and ampicillin/sulbactam are the best choice because of the highest susceptibility. In the beginning, the third-generation cephalosporin was used. However, one of the downsides is antibiotic resistance, unfortunately. In a UK review of sputum specimens from H. influenzas-positive patients with COPD. 67% of the patients experienced ampicillin resistance, and 46% displayed macrolide resistance. With over 52% of isolated being ampicillin-resistant, similar findings were found in research on children and adolescents in China [8]. Moreover, the period for the treatment depends on the velocity of rehabilitation.

4.2. Meningitis

For those typical meningitis patients, those antibiotic medicine is recommended. For example, Ceftriaxone, Ceftazidime, Cefotaxime, Ampicillin-Sulbactam, Fluoroquinolones, and Azithromycin were given through the parenteral route in one week [9]. In addition, Dexamethasone is also an indispensable part of the clinical trial as it will act as an auxiliary treatment to eliminate cerebral edema, the inflammation of the meninges. While they also need to manage the other complication at the same time. Like seizures and abscesses. In this process, approximately four days in a course are given at a dose of 0.6mg/kg/day. However, antibiotic medicine like Ampicillin and Cefuroxime do not recommend [3].

4.3. Epiglottitis

One way is called helping with breathing. In this process, three ways are provided, putting on an oxygen mask or using intubation. (A breathing tube is inserted into the windpipe through the nose or mouth). In addition, using a needle cricothyroidotomy (Putting a needle into the windpipe). The other way is taking

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two Antibiotics: Broad-spectrum antibiotics. (Quick treatment before diagnosis) and a More-targeted antibiotic. (Depending on which type of bacteria causes the epiglottitis.) [10].

4.4. Sepsis

For those typical Sepsis patients, the following medications can be used. One is called using insulin for blood sugar levels, or painkillers. The other is taking antibiotics which is similar to Epiglottitis. Or adding fluids to veins: intravenous fluids. Finally, using vasopressors if those patients suffer from low pressure after injecting that antibiotic, Vasopressors will help to maintain the level of their blood pressure [10].

5. Hib vaccine

5.1. Hib polysaccharide vaccine

One of Finland's investigations showed that PRP is affected by age, whereas transmission does not be interrupted. In addition, plain polysaccharide vaccinations do not cause immunologic memory or stimulate a booster response with repeated exposure. Thus, scientists turn to designing the conjugate Hib vaccine [11].

5.2. Hib Conjugate vaccine

The chemical manufacture of a Hib saccharide antigen led to the design of a conjugate vaccination against Hib. Thus, the Polyriboslribitol phosphate (PRP) capsule, a crucial component of the vaccine structure, and a selected protein are combined to form the conjugate vaccine. In this mechanism, this causes a sufficient T-cell response (figure 2). Additionally, those proteins needed T cells to activate the vaccine's antibody to generate a response, followed by the conversion of IgM to IgG. The T-helper cell will work during this procedure. After that, B cells will develop memory cells and respond more frequently after the second infection. Toll-like receptor 9 (TLR9) agonists have been used as adjuvants to assist in making up for immunodeficiency experienced late in life or adolescence. Adjuvants can further minimize immune interference triggered by polyvalent conjugate vaccines by, among other things, blocking the B- or T-cell-dependent carrier. Thus, adjuvants play an essential role in this vaccine [12].

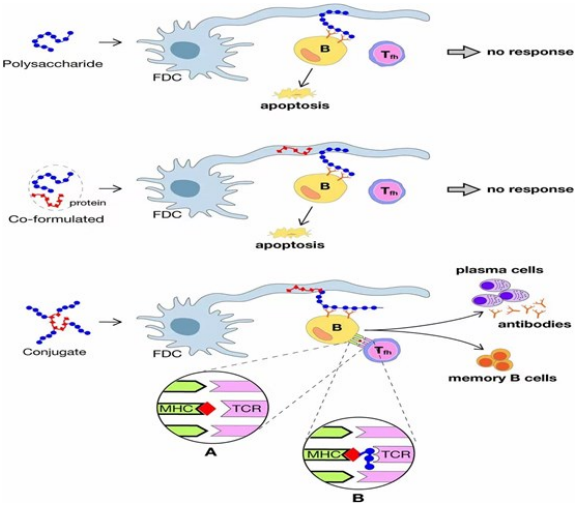

Figure 2. Interaction of polysaccharide and conjugate vaccine with FDC B and T helper cells in the GCS [12].

Three types of Hib conjugate vaccine have been developed. Oligosaccharide PRP, Native PRP and Synthetic PRP, respectively. They function by combing different fragments of CPS. Until the quantity of anti-PRP antibodies is enough, the vaccine works. The Oligosaccharide PRP method successfully

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eliminates three prerequisites. For example, pathogenic strains of H. influenzae do not need to be cultured, PRP does not need to be isolated and bacterial contaminants, such as toxic lipooligosaccharides, do not need to be separated. Oligosaccharides combine with protein carriers utilizing a wide range of coupling techniques. Tetanus toxoid (TT), diphtheria toxoid (DT), and OMPC protein are typical names for these protein transporters. Furthermore, they use aluminium hydroxide or phosphates as adjuvants. In order to solve issues with the processing of native PRP and its low-molecular-weight fractions, work is currently being done to build a synthetic method for spacer-armed oligosaccharides that are structurally similar to immunodominant PRP fragments [13]. One piece of experimental research indicates that Alcaligenes lipid A is an ideal adjuvant for this conjugate vaccination when utilized in the Synthetic PRP process. Alcaligenes lipid A, on the other hand, is only active when TI antigen-specific antibody synthesis is also present with TD antigen. The lgG specific to PRP will then develop. T-cells are not affected by it. On the other hand, the development of antibodies and B-cell proliferation will be boosted [14].

2008 saw the development of the pentavalent (DTwP-HB-Hib) quinvaxem vaccine. Because it is extremely immunogenic and induces strengthened antibody responses after primary immunity in babies at 2, 4, and 6 months of age, as demonstrated by one of the studies, individuals only need to inject one type of vaccine to prevent three forms of disease [15]. Nevertheless, it took four or five doses of this vaccination to ensure that approximately 90% of kids have protective levels of anti-diphtheria toxoid (DT) and anti-tetanus toxoid (TT) IgG [15].

Another vaccination now offered is the Pentabio® (Bio Farma) combination vaccine, a DTP-HB-Hib vaccine produced as a homogenous solution. According to the study, a three-dose of its regimen utilising a distinct hepatitis B source is positively received and immunogenic. By using data, they were able to demonstrate that, 28 days following the final treatment, all babies had anti-diphtheria and anti-tetanus titers less than 0.01 IU/mL, 100% had anti-HbsAg titers less than ten mIU/mL, and 96.1% had anti-PRP-TT titers less than 0.15 g/mL. When given the pertussis vaccine, 82.5% of recipients reacted well [15]. The child was advised to inject the first dose at two months of age and complete the entire immunisation process at 12 to 15 months old. Three doses are required as it will function well; however, if they miss the appropriate time, injecting more than standard is advised. The Hib vaccine is also suggested for people with sickle cell disease, prior to spleen removal surgery, or after a bone marrow transplant. For individuals infected with HIV, however, vaccination against Hib is not advised.

5.3. Hib vaccine prons and cons

The Hib vaccine has its advantages and disadvantages. For the benefits, the Hib vaccine has high effectiveness and safety. The roll-out of the Hib conjugate vaccination resulted in a 99% decline in Hib-related disease by the beginning of the 1990s. In addition, the FDA approved the Hib-conjugate vaccine used for children under five years old. The hib-conjugate vaccine functions with the other type of vaccine at one time. For instance, DTaP-IPV/Hib A study illustrates that because Hib-conjugate vaccines can protect against two or three dangerous diseases, the incidence of meningitis and epiglottitis in early childhood has significantly dropped [16]. Thus, the safety and efficacy of the Hib vaccine are assured. For the drawbacks, the number of doses needs to be injected is more than three times. For instance, three doses for PedvaxHIB, ActHIB, and Hiberix need four injects in the whole process of vaccination [17]. In addition, no oral vaccine is provided in clinics nowadays. Thus, Children under five years old need to suffer from muscle injections at the authority clinic. On the other hand, side effects will stimulate after vaccination. Like, an allergic reaction includes redness or swelling in your arms [18]. In addition, vaccines do not cover all strains.

6. Conclusion

In western China, less than 5% of people have received the Hib vaccination, although it is widely used globally. Therefore, the first step in the future will be to increase vaccination rates and introduce them in nations with a significant Hib burden. The next stage might be to eradicate Hib's illness. The vaccine

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accessible to protect patients against infections brought on by non-B-encapsulated or non-typeable strains is also one of the ongoing trials for the future.

In summary, Haemophilus influenza is a nasty bacteria that causes several illnesses. The majority of kids under five years old will be most at risk. Therefore, this paper would like to draw attention to this "killer" and urge the government to expand vaccination programmes and permit extra funding so that children in underprivileged communities may receive vaccinations. This study included an overview of Haemophilus influenza, pathology, and the Hib conjugate vaccine, the most effective vaccination to ward off several illnesses brought on by H. influenza. Hopefully, Haemophilus influenzae will be eradicated in the future. Furthermore, such pains will no longer be experienced by all aged groups, especially newly born newborns.

Author contribution

All the authors contributed equally, and their names were listed in alphabetical order.

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