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An overview of the meningococcal disease and impact of the quadrivalent meningococcal conjugate vaccine

Asmaa Alrobai[1*]; Jehan Alrahimi[1,2]; Sahar El Hadad[1,2,3]

[1]Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia; [2]Immunology Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; [3]Research Center of Genetic Engineering and Bioinformatics, VACSERA, Cairo, Egypt

[*]Corresponding author E-mail: aahmadalrobai@stu.kau.edu.sa

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Abstract

Meningitis is an inflammation of the meninges, which are the three membranes that cover the brain and the spinal cord; which occurs when the fluid surrounding the meninges becomes infected. Meningitis is a life-threatening disease, particularly in older people and immunocompromised cases. The estimated annual numbers of meningitis cases in the industrialized countries are about 4-6 cases per 100,000 people. Meningococcal disease is caused by the bacterium *Neisseria meningitides*, which have A; C, Y, and W-135 serogroups. Immunization helps to protect the humans from infection, such as the meningococcal vaccine that protects from infection by A; C, Y, and W-135 serogroups. Meningococcal conjugate vaccines improve the immunogenicity potential, to prevent meningococcal disease. Several previous studies have documented the decrease in post-vaccination effectiveness induced by the meningococcal vaccines. However, effectiveness requires revaccination after a period of time from the first vaccination. The purposes of this article were to provide an overview of the meningitis disease, and demonstrate the effectiveness of the meningococcal conjugate vaccine.

Keywords: Meningococcal, Vaccine, Meningitis, *Neisseria meningitides*, Conjugate vaccine

1. Introduction

Meningitis is an infectious disease that leads to life-threatening effects if not treated (Zunt *et al*., 2018; Fuentes-Antrás *et al*., 2019). This disease occurs due to infection either by different species of bacteria such

as; *Streptococcus pneumonia* and *Neisseria meningitides* and\ or caused by viruses including *Enterovirus*; *herpes simplex* and *varicella-zoster*, which altogether represent the causal agents of about 50 % of the cases. Moreover, a previous study conducted by Griffiths *et al*., (2018) reported that *Hemophilus influenza*; *Listeria monocytogenes*, *Mycobacterium tuberculosis* and several other fungal spp. are other causal agents of meningitis disease. Meningitis induced by bacteria although is less common; however, is more life-threatening than viral meningitis, because bacterial infection may cause mental retardation in the untreated individuals; unlike the viral meningitis, which shows spontaneous improvement (Logan and MacMahon, 2008). Bacterial infection has been reported as more risky among immunocompromised patients (Adriani *et al*., 2015). Therefore, vaccination against bacterial meningitis may prevent and protect the people's that suffer from immunodeficiency diseases, such as cancer; diabetes and human immunodeficiency virus (HIV) (Adriani *et al*., 2015). Recently, CDC. (2020) reported that no vaccine is 100 % effective against all the meningitis pathogens, because each person has his own immunogenicity towards the vaccine. The objectives of this review were to cover the meningitis disease; study the effectiveness of meningococcal vaccination on the human immune response, and follow the advances of researches in this field.

2. Meningitis disease

Meningitis is a type of inflammation in the membranes (meninges) that surround and protect the central nervous system (CNS), which consists of the brain and the spinal cord (Griffiths *et al*., 2018). Bacterial meningitis is associated with substantial-high mortality and morbidity rates (van de Beek, 2012). Most of the mortality cases occur in the bacterial meningitis (Griffiths *et al*., 2018), caused mainly by; *Streptococcus pneumonia* and *N. meningitides*. According to Pomar *et al*., (2020), approximately about 4-6 of infected cases per 100,000 adults are recorded annually in the industrialized countries. Older people are more vulnerable to infection by bacterial meningitis than younger ones (Domingo *et al*., 2013). Transmission of the bacterial meningitis in infants takes place either from the mother through the birth canal and\or from another person carrying out the pathogenic bacteria (van de Beek *et al*., 2016).

According to the previous work conducted by Tzeng *et al*., (2014), bacterial meningitis is transmitted in adults through contact with the infected individual's respiratory secretions during coughing or sneezing. On one hand, infants infected with bacterial meningitis have different symptoms, such as irritability; poor feeding, high fever, respiratory distress, pale skin and constant cry or hypotonia. On the other hand, the affected adults suffer from common signs of headaches; fever, neck stiffness, rash and altered mental status (van de Beek *et al*., 2016).

N. meningitides (Fig. 1) are Gram (-) bacteria that have 13 serogroups; defined according to the capsular polysaccharides and the main virulence factors (Harrison *et al*., 2013). Almost all these bacterial infections are caused by A, B, C, W135, X, and Y serogroups (Pizza and Rappuoli, 2015). *N. meningitides* usually colonizes the human nasopharynx; by adhering to the mucosal surface and exploiting the nutrients present in the mucosa. Moreover, the bloodstream invasion could happen when N. meningitides cross the epithelial cell layer of the nasopharynx; however, this crossing rarely occurs (Soriani, 2017).

A previous study of Herold *et al*., (2019) documented that the central nervous system (CNS) is protected by meninges; composed of three layers mainly, the dura; the arachnoid and the pia. The meningitis bacteria infect the CNS by colonizing any mucosal surface, and then invade the bloodstream to bypass the immunity system barrier. Once the bacteria reach the bloodstream, it can cause severe inflammation in CNS on crossing both of the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB), which all play important roles in protecting the brain (Herold *et al*., 2019).

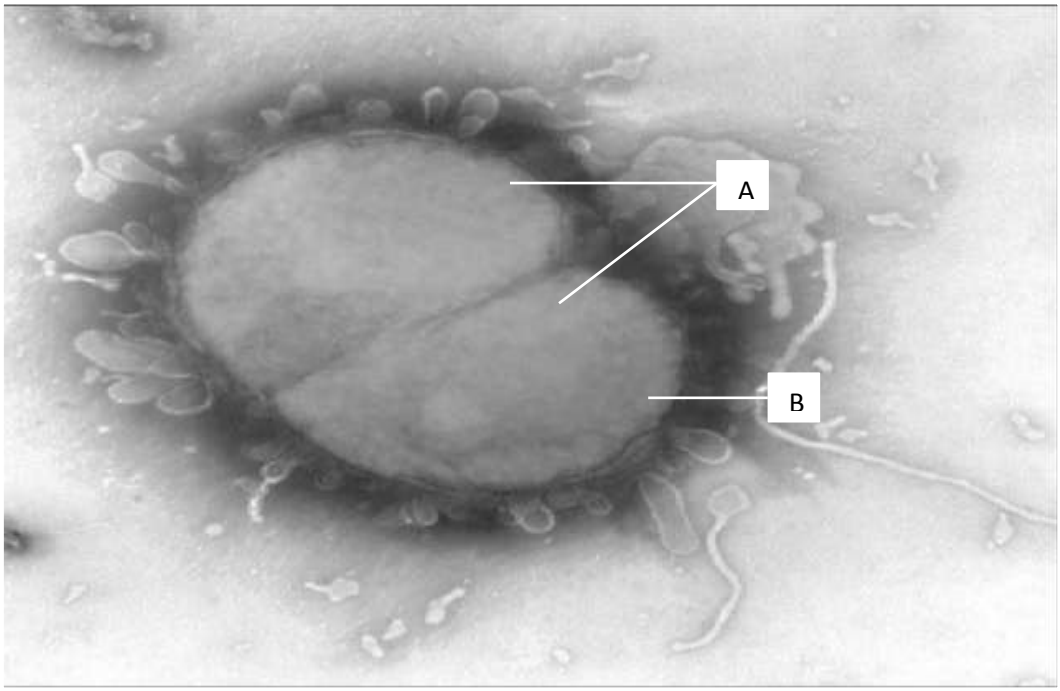

Fig. 1: *Neisseria meningitidis* morphology under an electron microscope. **A.** The bacterium is present as diplococcai. **B.** Bacterial capsule, adopted by Gorringe and van Alphen, (2009)

2.1. Epidemiology

The incidence of bacterial meningitis caused by A, B, C, W135, X, and Y serogroups varies widely worldwide (Mohamed and Abubokr, 2017). Serogroups B and C cause most of the meningitis diseases in the North and South America, Europe and Australia, while serogroup A is more frequent in the sub-Saharan Africa and Asia. Although less common; increased outbreaks of serogroup Y was recorded in North America, South America and South Africa, and most recently; emergence of serogroup W-135 was detected in the Middle East and Africa (Fig. 2). Besides, serogroup X disease has emerged in sub-Saharan Africa (Ceyhan *et al*., 2016).

Despite the decrease in incidence of cases suffering from the bacterial meningitis, resulted from the implementation of meningococcal polysaccharide and conjugate vaccines; almost 1.2 million cases of meningococcal meningitis still occur worldwide every year (Ceyhan *et al*., 2016).

2.2. Symptoms and diagnosis

Cerebrospinal fluid (CSF) sample is commonly collected by performing Lumbar puncture (LP). Usually, before LP and antibiotics; the start of using computed tomography (CT) led to the delayed disease treatment. Moreover, the use of antibiotics before LP and CT will decrease the yield of CSF culture. Once CSF is collected, a Gram stain method should be carried out to detect the bacterial meningitis and identify the antibiotics used for treatment (Young and Thomas, 2018). In addition, CSF analysis is also used to identify the leukocyte count. According to Griffiths *et al*., (2018), bacterial meningitis has a leukocyte count of more than 1000 cells/ µl with a neutrophilic predominance,

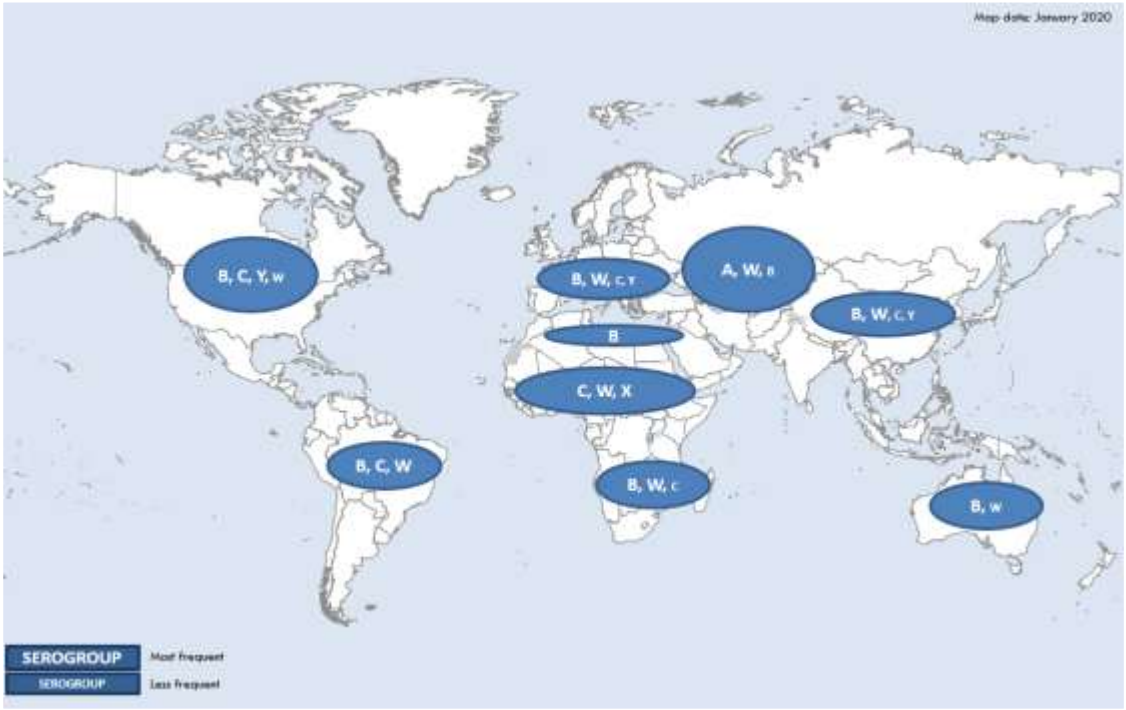

Fig. 2: Worldwide distribution of meningococcal serogroups; A, B, C, W135, X and Y. Bold serogroups show more frequent distributions (WHO. 2019)

while viral meningitis has less than 1000 cells/ µl with a lymphocytic predominance (Young and Thomas, 2018). However, in some cases; including children with positive pathogens detection, the immunocompromised patients and those pre-treated with antibiotics were characterized by the absence of pleocytosis (Young and Thomas, 2018).

Furthermore, CSF culture is advised to diagnose 70-85 % of the meningitis cases before antibiotic treatment, because the antibiotics lead to sterilization of the CSF from meningococci within 2-4 hours (Griffiths *et al*., 2018). The CSF glucose levels may be reduced in the patients suffering from bacterial meningitis. However, measurement of the blood glucose\ CSF glucose ratio can be used during the process of diagnosis. The average ratio of blood glucose\ CSF glucose may be less than or equal to 0.5 for the recorded cases of bacterial meningitis (Young and Thomas, 2018).

2.3. Polymerase chain reaction (PCR)

The polymerase chain reaction (PCR) technique is used to reveal the presence of bacteria through detecting their nucleic acid sequences (DNA, RNA) within the CSF (Griffiths *et al*., 2018). The *in vitro* amplification of DNA exploits two specific oligonucleotide primers and a heat-stable DNA polymerase. The amplification technique of the DNA is performed through three steps. First; the double-stranded DNA separates into two single strands by heating to 95°C, while the second step involves the primers anneals to the template DNA at the lowered temperature of 50°C. The third step is that DNA polymerase extends when the temperature rises to 72°C, in order to form a new DNA strand. The PCR products can be visualized by using an agarose gel Electrophoresis, stained with Ethidium bromide and then observed under ultraviolet (UV) light (Mullis *et al*., 1986). Moreover, this technique can give results to

the patients treated with antibiotics before LP (Griffiths *et al*., 2018).

2.4. Quantitative Real-time polymerase chain reaction

Quantitative real-time PCR (qRT-PCR) is a laboratory technique combining Real-Time PCR (RT-PCR) with Quantitative PCR (qPCR) that is used to detect gene expression. The method of qRT-PCR uses RNA as a template to generate single-strand complementary DNA (cDNA) by using a reverse transcriptase enzyme, which is then amplified through the DNA polymerase. At the same time, qPCR quantifies PCR products by using fluorescent technology (Adams, 2020). Synergy brands green (SYBR) is a fluorescent intercalating dye, which is bounded to the minor groove of the double stranded DNA (dsDNA), to detect the amplicon production (Yang *et al*., 2016).

3. Immunity and meningitis

According to Wang *et al*., (2016), the innate immune system is one of the immune strategies found in vertebrates, which provides a short-term defence mechanism after exposure to almost any microbe, and allows the adaptive immune system to initiate an antigen-specific response. A previous study of Hanke and Kielian, (2011) reported that the innate immune system detects the pathogens' presence by recognizing the molecules unique to several groups of related microorganisms called the pathogen-associated molecular patterns (PAMP). These PAMPs can be identified through the pattern recognition receptors (PRRs) such as the Toll-like receptors (TLR), which can stimulate the human adaptive immunity. Furthermore, TLR4 can recognize PAMP such as lipopolysaccharides (LPS) from Gram (-) bacteria (Hoshino *et al*., 1999; El-Zayat *et al*., 2019). Meningococci can survive the host defence by developing several immune escape strategies such as a capsule, which is up-regulated during the bloodstream invasion. However, as shown in Fig. (3), absence of the capsule's down-regulation allows meningococcal adhesion to the mucosal surface to form colonies and biofilms (Pizza and Rappuoli, 2015). Invasion of the meningococci triggers the release of cytokines, such as Interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) (Waage *et al*., 1989). A cytokine is a molecule that affects the immunity regulation by mediating the interactions between the cells. Interleukins are types of cytokines involved in cell's signaling (Hackett *et al*., 2001). TNF-α is the most prominent and studied cytokine during the bacterial meningitis, and it can aids in diagnosis (Coutinho *et al*., 2013). This pro-inflammatory cytokine shows an elevated CSF level during the early stages of the disease (Vivas *et al*., 2017).

Furthermore, after 1-2 h of injection of the meningococcal lipopolysaccharide (LPS), the animal models showed the maximum level of TNF-α; however, it became undetectable after 18-24 h. On the other hand, elevated levels of TNF-α can be detected in the human patients during the first 48 h of the disease (Coutinho *et al*., 2013). Moreover, IL-6 is another pro-inflammatory cytokine that is released in high concentrations during infection, and can be used as a valuable marker for diagnosis of the bacterial meningitis. The crucial role of the pro-inflammatory cytokines is their up-regulation of the endothelial adhesion molecules, which allow the neutrophils and lymphocytes to flow from the bloodstream into the infection site (Takahashi *et al*., 2014).

4. Lymphatic system and immunity

The circulatory system constantly transports the blood fluid, which delivers the essential nutrients and oxygen into the body tissues. At the same time, the lymphatic vessels carry out the interstitial fluid to the lymph nodes (LNs), which can be returned to the blood. Consequently, Kastenmüller *et al*., (2012) documented that the LNs are lymphoid organs that act as filter-like structures that filter the lymph before returning to the blood, as demonstrated in Fig. (4). The lymph node's macrophages can phagocytose various materials such as microbial pathogens from the lymphatic fluid (Gray and Cyster, 2012).

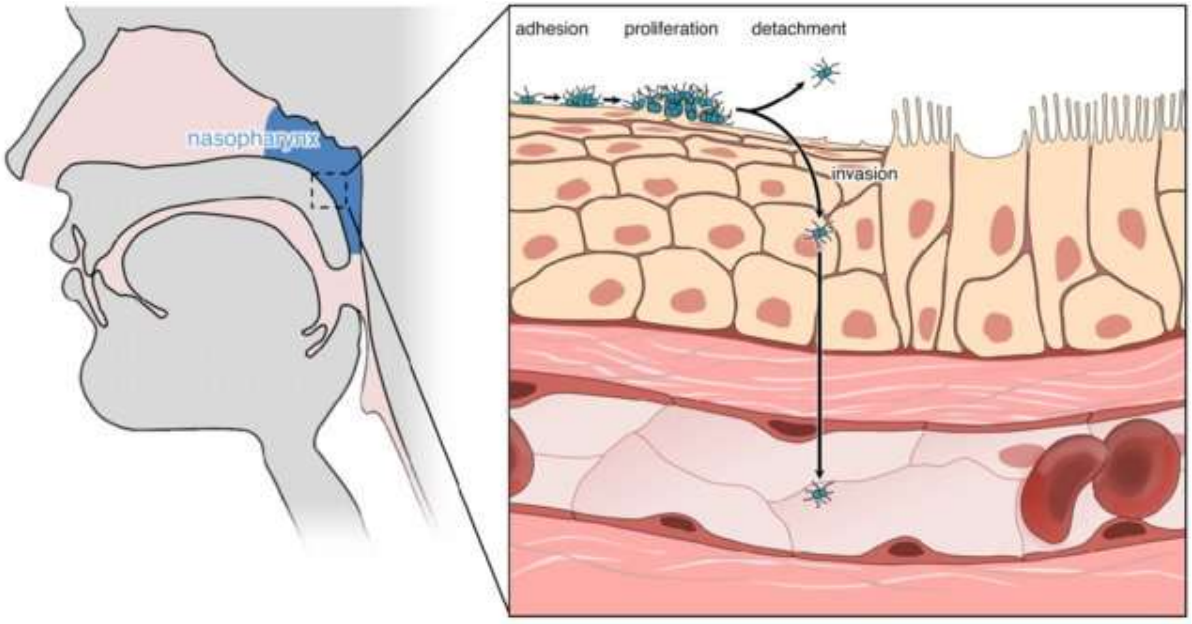

Fig. 3: Life cycle of the bacterial meningococcal disease. *N. meningitidis* adheres to the human mucosal surfaces to form colonies that cross the epithelial cells; to allow invasion through the bloodstream, adopted by Charles-Orszag, (2017)

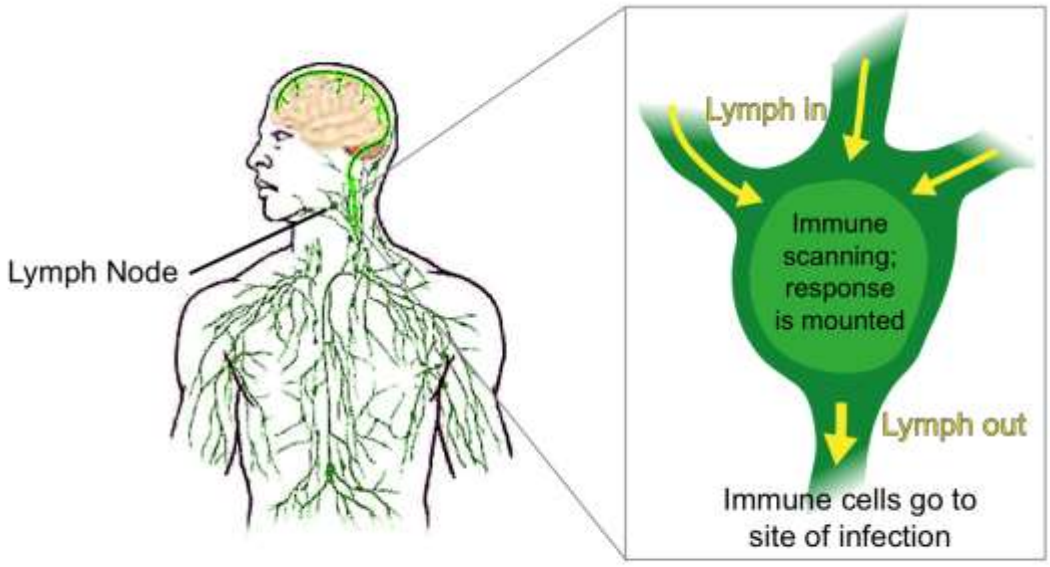

Fig. 4: Human lymphatic system. Lymph enters the lymph nodes for filtration before returning to the blood stream, adapted by Siwicki and Maurer, (2016)

Accordingly, during the dissemination stage through lymphatics; the pathogens need to escape from the lymph nodes back to the bloodstream (Bogoslowski and Kubes, 2018). As shown in Fig. (3), the most likely way for meningococci to enter the bloodstream is by penetrating the epithelium and drain to the lymph nodes, and then they spread to the meninges (Christodoulides *et al*., 2002). The dendritic cells (DCs) are antigen-presenting cells (APCs). When DCs become activated to start to capture the pathogens that enter the body, they put out the antigen on the cell surface, and then migrate to the draining lymph nodes (Fig. 4). Lymphocytes travel to the lymph nodes when become stimulated by the cytokines of DCs, where the lymphocytes can be activated and proliferated for the specific antigen. According to Wee *et al*., (2011), IL-6 and TNF can stimulate the immune response by regulating the traffic of lymphocytes and APCs; via sequestering them for several hours in the local lymph nodes for recruitment. Moreover, the Toll-like receptors (TLRs) are Pattern recognition receptors (PRRs) such as TLR4, which are receptors for the LPS. Garrafa *et al*., (2011) reported that the lymphatic endothelial cells (LECs) derived from lymph nodes (Ln-LECs) express TLR4. On the other hand, Owen *et al*., (2018) revealed that Interleukin-2 (IL-2) is a cytokine that is important for development of the regulatory T cells (Tregs), and has a role in the immune homeostasis. The T-cells and dendritic cells (DCs)-derived IL-2 in the mesenteric lymph nodes are critical for maintaining the abundance of the Tregs.

5. Risk factors of meningitis

Diseases such as cancer; HIV infection and diabetes, can all disrupt the immune system functions, and increase the risks of invasive infections, including meningitis.

5.1. Cancer

Cancer is one of the most significant global burdens of illness, which is characterized by uncontrolled cell proliferation. Every year, millions of people worldwide are diagnosed having cancer, and more than half of those patients eventually die (Hassanpour and Dehghani, 2017). Recently, a study conducted by Sung *et al*., (2021) reported that lung cancer is the most common cause of death in men; followed by prostate and colorectal cancer in terms of incidence, and the liver and colorectal cancer in terms of mortality. Breast cancer is the most frequently diagnosed cancer in women and the leading cause of death; followed by colorectal and lung cancer in terms of incidence and mortality, respectively. According to Anand *et al*., (2008), cancer can be caused either due to internal factors such as genetic mutations; hormonal and immune conditions, or due to environmental (external) factors including; tobacco, alcohol, diet, radiation, environmental pollution and infectious agents. However, patients suffering from meningitis and cancer have more subtle clinical symptoms and higher mortality rates than patients without cancer (Pomar *et al*., 2017). Moreover, patients with active cancer and lower leukocyte counts in the CSF are more susceptible to being infected with *L. monocytogenes* (Costerus *et al*., 2016).

5.2. Human immunodeficiency virus (HIV)

Infection with HIV is caused by one of two retroviruses (HIV-1 and HIV-2), which destroy the $CD4^+$ cells and compromise the cell-mediated immunity (Barré-Sinoussi, 1996). Both retroviruses cause AIDS, but the main difference is that HIV-2 infection progresses to immunodeficiency more slowly than HIV-1 infection and is localized in West Africa; unlike HIV-1, which is found all over the world (Nyamweya *et al*., 2013). Nowadays, approximately 38 million people live with HIV, and tens of millions more have died since the widespread of this disease; as reported by UNAIDS. (2020). People infected with HIV are 6 to 324 times more likely to develop an invasive pneumococcal infection (Bliss *et al*., 2008). However, compared to the general adult populations; people with HIV infection have a greater rate of meningococcal disease (Harris *et al*., 2016). Moreover,

Simmons *et al*., (2015) added that invasive meningococcal disease is dramatically elevated in HIV-positive children and adults; giving evidence to consider HIV as a risk factor for meningococcal immunization.

5.3. Diabetes mellitus

Diabetes mellitus (DM) is a chronic disease characterized by increased blood glucose level (hyperglycemia), and the disease is commonly divided into type 1 (T1D) and type 2 diabetes (T2D). Insulin injection allows tissue cells to take up and degrade glucose (Dong *et al*., 2018). However, T1D causes insulin deficiency due to an autoimmune disorder that destroys the β-cells in the pancreas (Ndisang *et al*., 2017). This destruction is attributed to the cell-mediated immune response mediated by islet-infiltrating lymphocytes and macrophages. The macrophages secrete toxic cytokines that are able to damage the β-cells and $CD8^+$ cytotoxic lymphocytes through pore formation (Zóka *et al*., 2013). In T2D, although the pancreatic β-cells produce insulin; however, the body cells cannot utilize it effectively (Ndisang *et al*., 2017). Both of genetic and lifestyle factors are linked to T2D (Li *et al*., 2020). Both types of DM increase the rate of microbial infections, especially by the bacterial pathogens. A study conducted by van Veen *et al*., (2016) revealed that DM can cause immunodeficiency through decreased efficacy of the cell-mediated immunity, and through functional defects in the granulocytes, monocytes and lymphocytes. Thus, DM patients are more susceptible to developing bacterial meningitis compared to the non-diabetic patients. According to Pomar *et al*., (2020), the International Diabetes Federation (IDF) expected that by the year 2035; almost about 590 million individuals would have diabetes. Consequently, this disease will be a high-risk factor for meningitis (van Veen *et al*., 2016).

6. Treatments and protections from meningitis

The meningococcal disease results from several factors, such as; the microbial virulence factors, environmental conditions and susceptibility of the individual's immune system to microbial infection (Rouphael and Stephens, 2012). Meningitis disease must be diagnosed promptly to determine the proper therapeutics protocol, which will be either antibiotic or supportive therapy (Dexamethasone). The treatment protocol of meningitis will depend on the infection's causes (Mehrdadi, 2019). The type of antibiotics used to treat the bacterial meningitis is based on the species of the causal bacteria, which are identified using the diagnostic strategies. Simultaneously, for the patient with suspected bacterial meningitis, dexamethasone antibiotics should be given (Griffiths *et al*., 2018). Most viral meningitis patients need supportive care because there are no specific treatments for them (Griffiths *et al*., 2018). Transmission of meningitis almost occurs through contact with the affected individual's respiratory secretions during coughing or sneezing. People who contact meningitis patients' can protect themselves by following some behavioral measures and\or by taking antimicrobials that provide short-term protection, such as Ceftriaxone and Rifampin antibiotics (Mehrdadi, 2019).

The meningococcal vaccines include polysaccharide and polysaccharide-protein conjugate vaccines, which give protection against A, C, W135 and Y serogroups (Yezli *et al*., 2016). Several previous studies including Bliss *et al*., (2008); Poolman and Borrow, (2011); Zhao *et al*., (2020) have reported that the polysaccharide vaccine is T-cell independent antigens, which stimulate the B cells responses only, and do not cause long-lasting immunity. On the other hand, the polysaccharide-protein conjugate vaccine is a T cell-dependent antigen. The T cells are activated through the interaction with the B cells surface molecules, causing long-lasting immunity. Accordingly, the previous study conducted by Zhao *et al*., (2020) recorded that the polysaccharide conjugate vaccine improves the human immunogenicity.

Millions of Muslims come to Saudi Arabia from different countries and gather annually in Makkah and El-Medina (Yezli *et al*., 2016). Accordingly, the long periods spent at Al-Hajj pilgrim

sites, in addition to the extreme heat; crowded accommodation, traffic jams and the generally advanced age of pilgrims, amplify the rate of *N. meningitides* transmission (Ahmed *et al*., 2006). To reduce the spread of meningococcal disease during Hajj and Umrah; the Kingdom of Saudi Arabia imposed preventative measures. By 2002, vaccination with the quadrivalent (serogroups A, C, W and Y) meningococcal polysaccharide vaccine becomes a prerequisite to obtain a visa for Hajj and Umrah (Yezli *et al*., 2016). Accordingly, the incidences of meningitis in Saudi Arabia dropped significantly, as indicated in Fig. (5).

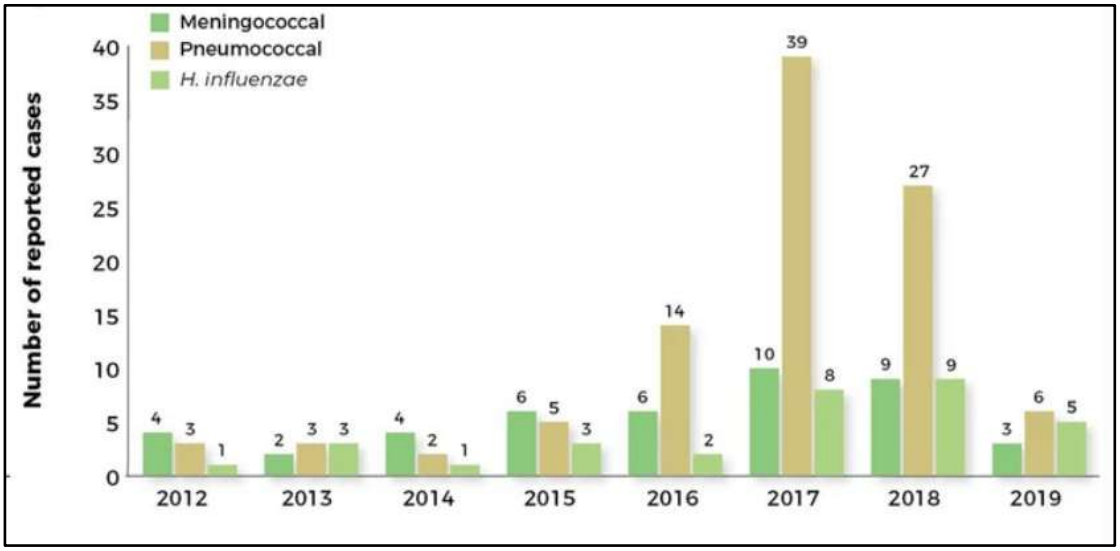

Fig. 5: The meningococcal, pneumococcal and *H. influenzae* incidences during 2012-2019. The digit above each column represents the recorded number of vaccine-protected cases per year, adopted by Badur *et al*., (2021)

A recent study conducted by Tobaiqy *et al*., (2020) showed that the pilgrims' are imposed behavioral and practice issues, including immunizations; especially the quadrivalent meningococcal vaccine. Another issue is wearing face masks in crowded areas; especially during the COVID-19 pandemic. Moreover, a previous study has reported the effectiveness of post-vaccination by Meningococcal conjugate vaccine (MCV) impaired within 3-8 years, and therefore needs another booster dose (Cohn *et al*., 2017). Another previous study conducted by Elias *et al*., (2013) found that the polysaccharide vaccines' immune response is weak in infants, unlike the polysaccharide conjugate vaccines. Moreover, the average duration of protection using the meningococcal polysaccharide vaccine is about 10 years; however, its effectiveness could fall below 10 years. The W135 serogroup vaccination offers a period of protection less than 5 years, so the treated person needs re-immunization (Elias *et al*., 2013).

6.1. Meningitis vaccine

Vaccines are made from inactivated or attenuated pathogens. The principle of vaccination is to stimulate the immune response of the human's body against antigens from specific pathogens. Moreover, the vaccine's immunization usually helps to reduce the spread of microbial infections (Lahariya, 2016). Undoubtedly, several evidences showed that vaccines' effectiveness outweighed their risks; including preventing the morbidity and mortality caused by the infectious diseases (Andre *et al*., 2008). Another study of Mad'ar *et al*., (2011) that was conducted within a

period of 9.5 months; revealed that 402 patients with DM were vaccinated without any increased risks of side effects.

In conjugate vaccines; the meningococcal bacteria have polysaccharides capsule covalently bound to the carrier proteins (Harrison *et al*., 2013). However, Menactra vaccine for serogroups ACWY (MenACWY-D) of the meningococcal bacteria is the first quadrivalent meningococcal conjugate vaccine, which is composed of four meningococcal capsular polysaccharides conjugated with the diphtheria toxoid protein. MenACWY-D can induce the T cell-dependent immune responses; increase the antibody avidity and the immunological memory (Pina *et al*., 2012). In the serum, the meningococcal vaccine causes the immunoglobulin G (IgG) antibodies to prevent the invasive meningococcal disease (Bårnes *et al*., 2016). Meanwhile, the vaccines do not provide complete protection for the individuals, especially for the immunocompromised patients suffering from diseases such as DM (WHO. 2012).

6.2. Improving the meningitis vaccine

It is well known that the immune response to vaccines varies between individuals. Recent evidences suggested that administration of the probiotics close to vaccination; influences the immune response (Zimmermann and Curtis, 2018). The World Health Organization (WHO) defined probiotics as living microorganisms that have beneficial effects on their hosts when consumed in adequate amounts (Reid *et al*., 2019). The most common probiotics mainly include; *Lactobacillus* and *Bifidobacterium* spp. (MacDonald and Bell, 2010). Probiotics are generally considered safe for most people; free from long-term adverse effects, and have positive impacts on treatment of the digestive, respiratory and immunological diseases (Prakash *et al*., 2011). According to Rolfe, (2000), the probiotic microorganisms have 4 beneficial effects mainly; (1) The production of pathogen inhibitory substances such as organic acids that inhibit the growth of pathogenic bacteria; (2) Blocking adhesion sites of the pathogenic bacterial cells; such as those that occur in the gut where the probiotics are attached to the epithelial cells; (3) Nutrient competition through consumption of the nutrients that would have been utilized by the pathogenic bacteria; (4) Modulation of the immune responses.

The first evidence that giving the infants *L. casei GG* as a probiotic before the oral administration of a rotavirus vaccine increases the serum immunoglobulin was recorded in 1995 (Isolauri *et al*., 1995). Similarly, a previous study carried out by MacDonald and Bell, (2010) on adult volunteers who started taking the probiotic a week before the oral polio vaccine; reported higher levels of the serum IgG and IgA. Other recent study of Gupalova *et al*., (2019) developed a new pneumococcal vaccine; by constructing a recombinant probiotic strain with a pneumococcal antigen. In addition, the same authors deduced that vaccination with live probiotics can stimulate the production of IgG and IgA. Besides, probiotics may positively induce the recovery of secondary bacterial infections such as those of *N. meningitides* and Pneumococci; caused primarily by the influenza infection (Belkacem *et al*., 2018). Furthermore, a recent study showed that the probiotic bacteria can enhance the B cells and the antibody responses (Abdo *et al*., 2019). Another research conducted by Bianchini *et al*., (2020) indicated that T1D pediatric patients who were administrated the probiotic *L. rhamnoses GG* (LGG) with a quadrivalent inactivated influenza vaccine (QIV); have modified immunity functions through reduced responses of the inflammatory cytokines (IL-6 and TNF-α). Recently, Aldahlawi *et al*., (2021) reported that *Saccharomyce*s probiotics recorded beneficial effects in the diabetic rates; through increasing the expression of the pro-inflammatory cytokines in the rats, after they were immunized with the influenza vaccine.

Conclusion

It is extremely surprising that effective and viable vaccinations against meningococcal disease have been recently developed. Meningococcal conjugation vaccines are critical in protecting the humans from

meningitis infection. Despite the proven efficacies of vaccination, their effectiveness is decreasing with time and need a booster dose. Numerous studies have shown that probiotics in general increase the effectiveness of the vaccines. However, a better understanding of the host immune response to probiotics and meningitis vaccines helps to improve the effectiveness of vaccines; especially in the immunocompromised patients. More advanced researches are required to extend understanding of the relationship between meningitis infection and vaccine administration.

Conflict of interests

No conflict of interests exists.

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Ethical approval

Non-applicable.

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