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Vaccination Across Borders: A Historical Overview of Travel-Related Immunization

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Abstract

In travel medicine, vaccinations play a crucial role in both protecting passengers and preventing the spread of diseases that can be prevented by vaccination in both the travelers' home countries and the places they go to. The first smallpox vaccine, created by Edward Jenner, was initially made available in 1796, marking the beginning of travel-related vaccination. Typhoid, Rabies, and cholera vaccines were created after this discovery, albeit it took over a century to make such a substantial advancement.Travelers now have access to vaccinations for hepatitis A, yellow fever, poliomyelitis, tetravalent meningococcal disease, and poliomyelitis as the 20th century came to a close. To make it easier for tourists to prove their immunizations, the International Certificate of Inoculation and Vaccination was developed in 1933. Nowadays, in addition to following the rules outlined in the 2005 International Health Regulations and the unique requirements of other countries, passengers receive vaccinations based on individual risk assessments. The COVID-19 pandemic's appearance was of particular significance because it ignited a never-before-seen rush to create vaccinations. The first COVID-19 vaccinations received emergency use authorisation to stop the spread of the virus within a year of the pandemic's announcement. The verification of COVID-19 vaccination status has been widespread, especially in foreign travel, since the spring of 2021, while confronting a number of practical and ethical problems. In this article, we provide a summary of the historical development of travel-related vaccinations with a focus on those for which vaccination documentation has been or is still required.

Keywords: travel vaccine, Yellow Fever, Smallpox, Hepatitis A, Japanese Encephalitis.

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Introduction

The widespread implementation of routine vaccination programs in the latter half of the 20th century stands as one of the most remarkable achievements in the history of public health, effectively thwarting millions of infections, fatalities, and enduring complications annually [1]. Beyond their impact on public health, vaccinations play a pivotal role in the realm of travel medicine. These not only safeguard international travelers but also serve as a bulwark against the introduction of vaccine-preventable diseases, both within the travelers' home countries and at their intended destinations [2,3]. Before embarking on international journeys, travelers undergo pre-travel vaccinations guided by a comprehensive risk assessment. This spectrum of vaccinations includes routine immunizations, suggested vaccines tailored to specific travel profiles, vaccinations mandated by the 2005 International Health Regulations (IHR), and those required by specific countries [2, 3, 4]. The origins of vaccinations can be traced back to ancient instances of infectious diseases in humans, particularly the early endeavors to induce immunity through the use of smallpox material. Historical evidence suggests that as far back as 1000 AD, the Chinese practiced smallpox inoculation [4, 5, 6]. Over time, vaccination policies were devised to address the movement of individuals across national boundaries. The formulation of vaccination policies has remained a central and enduring responsibility of the World Health Organization (WHO) via the framework of the International Health Regulations

(IHR). These regulations undergo periodic revisions in close consultation and collaboration with WHO's Member States, international entities, and other stakeholders, all aimed at effectively managing the global transmission of diseases [4]. The history of travel vaccines traces back to 1796 when Edward Jenner introduced the inaugural vaccine to combat smallpox in humans. This marked the inception of a significant journey in preventive medicine. The term "vaccination" derives from the Latin word "vacca," signifying cow, as Jenner harnessed cowpox material to establish immunity against smallpox [6]. Later, in 1881, Louis Pasteur extended the term "vaccination" to encompass preventative inoculation for both human and animal diseases, thus solidifying its broader application [7]. The year 1933 witnessed the establishment of the International Certificate of Inoculation and Vaccination during the International Sanitary Convention for Aerial Navigation, a pivotal step to facilitate travel and counter the trans-border transmission of infectious diseases [8]. The central objective was the protection of travelers and the containment of disease dissemination.

Beyond this core motive, various other rationales underlie the requirement for vaccination, including shielding specific demographics, containing outbreaks or epidemics, minimizing mortality rates, and pursuing disease eradication. Vaccination has emerged as a vital instrument to realize these aspirations. Presently, the World Health Organization (WHO) endorses globally accepted certificates as evidence of vaccination for entry into designated countries. These certificates encompass substantiation of yellow fever vaccination, obligatory for travelers entering certain regions, validation of meningococcal vaccination for Hajj pilgrims, and confirmation of poliomyelitis vaccination under specific circumstances [4]. In response to an internationally significant public health emergency that could imperil human populations, additional requisites for demonstrating vaccination status during travel might be instituted [4, 9]. In this narrative, our goal is to provide a comprehensive exploration of the historical trajectory of travel vaccines, with a particular spotlight on vaccines necessitating proof of vaccination, an element integral to the narrative of vaccination history. By closely examining the contextual evolution of travel vaccines, we endeavor to unravel their pivotal role in upholding global health during travel and curbing the trans-boundary diffusion of infectious diseases.

1. Yellow Fever Vaccines

Yellow fever (YF) is a disease effectively preventable through a live-attenuated vaccine known as 17D, which has been in use since the 1930s [8]. This vaccine, referred to as 17D, has demonstrated the capacity to provide long-lasting protective immunity for over 35 years with just a single dose. The pivotal determinant in conferring immunity lies in the presence of neutralizing antibodies. Despite the existence of a vaccine solution, yellow fever persists as a significant public health challenge, contributing to an estimated 109,000 severe infections and causing approximately 51,000 fatalities annually [10]. The combat against yellow fever faces the complication of supply and demand imbalances for the vaccine. Notably, outbreaks in 2016 and 2018 compelled the adoption of fractional dosing to meet the escalated demand for the vaccine. To combat this issue and curtail the yellow fever burden over the ensuing decade, the World Health Organization (WHO) introduced the "Eliminate Yellow Fever Epidemics" (EYE) initiative, which aims to alleviate the impact of yellow fever outbreaks [11].

The World Health Organization (WHO) plays a pivotal role in establishing guidelines to ensure the quality, safety, and effectiveness of the yellow fever vaccine. The vaccine's production is stipulated to exclusively occur in embryonated chicken eggs, and its safety is evaluated through non-human primate studies. These stringent criteria are outlined in accordance with WHO regulations [12]. Should any second-generation vaccines emerge, they would need to align with these WHO requirements, adhering to the production and safety assessment protocols applicable to the vaccine's development, particularly for use in regions where yellow fever is endemic. Presently, a variety of second-generation yellow fever vaccine candidates are undergoing diverse phases of development. These candidates must prove their safety and immunogenicity during clinical trials, demonstrating their non-inferiority to the established 17D vaccine. This comparison is crucial for potential future licensure. The impact of the historical 17D vaccine extends beyond its own use, influencing the landscape of global vaccines. This influence has led to the creation of multiple licensed recombinant chimeric live vaccines and vaccine candidates. These innovative vaccines involve replacing the structural protein genes of the original yellow fever 17D vaccine with genes from other viruses, like dengue and Japanese encephalitis. The versatility exhibited by the 17D vaccine continues to shape the trajectory of new yellow fever vaccines and holds the potential to extend its influence to combat other infectious diseases as well [13].

2. Smallpox Vaccines

The achievement of eradicating smallpox globally stands as a momentous feat, accomplished through the successful implementation of a vaccine. Although routine vaccination for the general populace is no longer deemed necessary, stocks of the variola virus, the causative agent of smallpox, remain securely stored in laboratories, giving rise to debates surrounding its permanent disposal. Furthermore, concerns have emerged about the potential existence of the variola virus beyond these controlled environments, thereby raising worries about its possible misuse as a bioterrorist weapon[14]. In response to these concerns, an extensive vaccination campaign was initiated in 2002, primarily targeting US military personnel, civilian healthcare practitioners, and first responders. The historically utilized live virus vaccine has demonstrated efficacy; however, it has also been associated with serious adverse events and infrequent fatal reactions, particularly in individuals with immunodeficiency and atopic eczema. Additionally, the conventional production method of this vaccine involved animal intermediaries, introducing risks of contamination and falling short of contemporary manufacturing standards. Consequently, ongoing research is dedicated to exploring alternative poxvirus vaccines, aiming to employ replication-defective viruses, gene-based vectors, and subunit strategies to amplify safety and immunogenicity[15]. Nonetheless, a predicament arises because, in the absence of a deliberate variola virus release, the assessment of novel candidate vaccines' efficacy is constrained to animal experimentation. This limitation poses challenges in the process of vaccine authorization. Despite being instigated by the bioterrorism threat, the overarching objective is for these innovative poxvirus vaccines to exhibit maximal effectiveness not only against other pathogenic orthopoxviruses like monkeypox but also to advance recombinant poxvirus-based vectors for both therapeutic and preventive purposes across a spectrum of diseases[16].

3. Hepatitis A Vaccines

The utilization of the hepatitis A vaccine holds a crucial position within travel vaccination protocols. Recent instances of annual hepatitis A infections in the United States have experienced fluctuations due to significant outbreaks associated with imported foods and urban transmission among homeless populations. This circumstance has prompted the consideration of extending the local implementation of the hepatitis A vaccine. Concerning hepatitis B, the vaccine is recommended for all adults, with a particular focus on healthcare workers. Since 1992, its administration has been extended to include newborns. A new two-dose hepatitis B vaccine, with each dose administered one month apart, has emerged and demonstrated heightened efficacy within adult populations. The hepatitis A virus (HAV) belongs to the Picornavirus family and is characterized as a nonenveloped positive strand RNA virus. Its primary mode of transmission is through the fecal-oral route, along with exposure to contaminated food and water sources. HAV infections typically lead to a self-limited inflammatory reaction in the liver, resulting in generalized symptoms. Nevertheless, in rare instances, it can progress to fulminant hepatitis and subsequent liver failure [17]. Over the past two decades, the Centers for Disease Control (CDC) have observed a noteworthy decline in the average annual count of HAV infections compared to the year 2000. Despite this overall trend, occasional fluctuations have arisen due to outbreaks linked to imported foods, drug usage, homelessness, and men who have sex with men. These occurrences have contributed to intermittent spikes in reported HAV infections [18]. In the United States, two licensed Hepatitis A antigen vaccines are available for individuals aged 12 months and older. These vaccines are HAVRIX® (manufactured by GlaxoSmithKline) and VAQTA® (manufactured by Merck & Co., Inc). The recommended vaccination schedule for HAVRIX® is 0, 6–12 months, whereas for VAQTA®, it is 0, 6–18 months[19]. Both vaccines have demonstrated the ability to elicit strong immunogenic responses, resulting in protective antibody levels in 94%–100% of adults one month after the initial dose, and 100% one month after the second dose. Similar rates of neutralizing antibodies have also been observed in children and adolescents. Moreover, protective antibody levels have been noted to endure beyond 20 years in healthy individuals.

Twinrix® (manufactured by GlaxoSmithKline) is a combination vaccine that offers protection against both hepatitis A and hepatitis B. The FDA first approved it in 2001, and it is administered according to a 3-dose schedule (0, 1, and 6 months) for individuals aged over 18 years. Twinrix's efficacy has been found to be on par with the effectiveness of existing single antigen hepatitis vaccines, assessed one month after completing the full series [20]. In Figure 1, the estimated age at which population immunity* to hepatitis A is reached in various countries is illustrated [21]. An alternative 4-dose schedule for Twinrix is also available, wherein doses can be administered at 0, 7, and 21 to 30 days, followed by a final dose at 12 months. This alternative dosing option may be particularly valuable when initiating Twinrix vaccination, and travel or potential exposure is anticipated before the administration of the second dose [22].

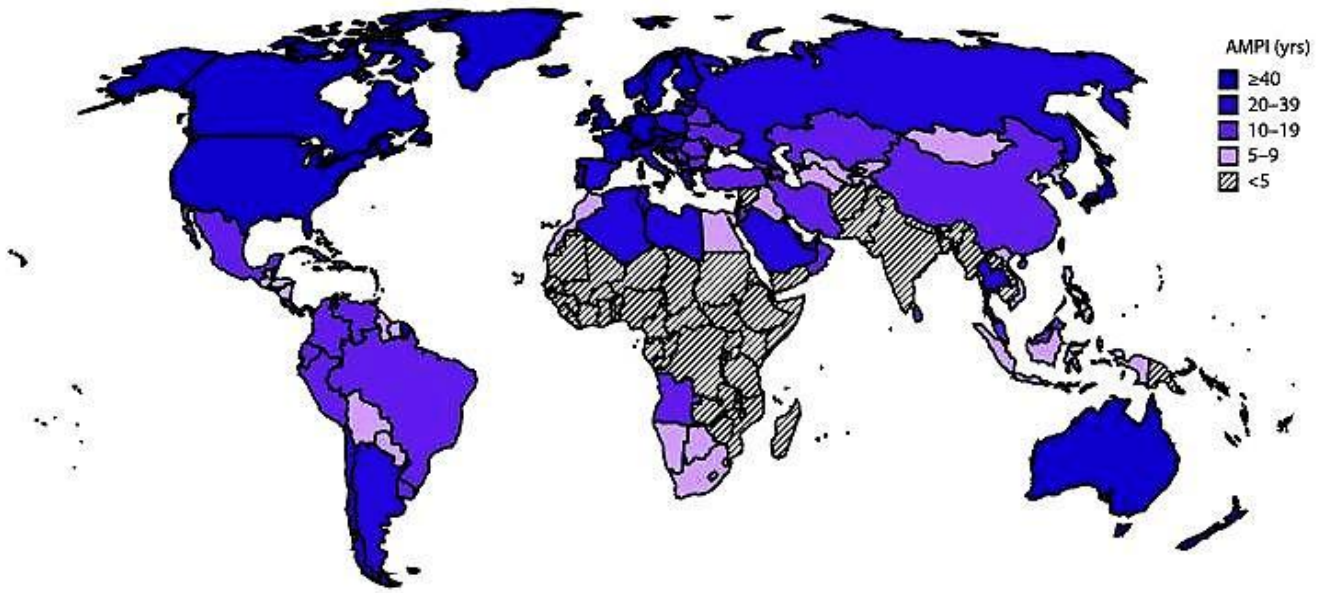

Figure 1: Estimated age at midpoint of population immunity* to hepatitis A, by country — 2015. [21]

4. Japanese Encephalitis Vaccines

Travelers embarking on journeys to 24 endemic countries in Asia should be mindful of the potential risk associated with Japanese encephalitis (JE). The Advisory Committee on Immunization Practices (ACIP) has recently issued updated guidelines concerning the utilization of Ixiaro, the inactivated Japanese encephalitis vaccine [23]. Japanese encephalitis is caused by a Flavivirus, closely related to the West Nile virus, and is primarily transmitted by Culex mosquitoes, which are active during the hours spanning dusk to dawn. The JE virus is naturally maintained by mosquitoes and animal hosts, with pigs and water birds being the primary carriers. Consequently, the risk of infection is most pronounced in rural farming regions, yet it also extends to urban and periurban areas across Asia. JE is endemic in a substantial portion of Asia, as well as specific zones in the western Pacific region. It ranks among the most prevalent causes of encephalitis in Asia. The transmission dynamics exhibit variation based on geographical location, with certain areas witnessing seasonal transmission, such as between May and September in northern Asia. In other regions like India and Southeast Asia, transmission corresponds with the monsoon season. Notably, in locations like Bali where rice paddies, pig farms, avian populations, and Culex mosquitoes are prevalent, JE transmission can transpire year-round. Travelers are advised to exercise vigilance and adopt appropriate preventive measures when journeying to these regions to mitigate the risk of contracting Japanese encephalitis.[24]

Japanese encephalitis (JE) has been documented in the Torres Strait Islands in northern Queensland, Australia. An intriguing observation is the significant demand for pork in Asian countries, which has spurred the relocation and establishment of pig farms in closer proximity to urban centers, facilitating easier distribution. This trend potentially contributes to the increased movement of the JE virus's risk. Travel clinic consultations play a pivotal role in helping individuals access country-specific information, including details about transmission periods, which can be found in the CDC Yellow Book. While JE infection is relatively infrequent among tourists, the estimated risk stands at approximately one in 200,000 per week of exposure. A minority of infections, less than 1%, result in symptomatic illness. However, such cases can lead to substantial morbidity due to acute encephalitis, presenting with diverse neurological symptoms. The case fatality rate for symptomatic instances can escalate to as high as 30%. Among survivors, 30% to 50% might endure enduring neurological, psychological, and cognitive impairments, encompassing polio-like weakness and lifelong seizure disorders. Travelers should be well-informed about these potential risks and take appropriate precautions, including considering vaccination, when planning journeys to areas with a heightened susceptibility to Japanese encephalitis [25]. Severe cases of Japanese encephalitis demand utmost attention due to

their gravity. Travelers venturing into areas where Japanese encephalitis (JE) is endemic should receive comprehensive guidance regarding mosquito bite prevention, particularly during the period from dusk to dawn when mosquitoes are most active. Deliberation over vaccination should also be a vital consideration, with recommendations tailored to a range of factors. These factors encompass the infection risk specific to the country, the urban or rural nature of the travel destination, involvement with farming regions, the prevalence of seasonal patterns, outdoor activities, the duration of the trip, and the potential for repeated travel. Given the substantial risks associated with symptomatic infections leading to severe complications or even death, in addition to the vaccine costs, these factors significantly influence decision-making processes. The Advisory Committee on Immunization Practices (ACIP) has updated their guidelines to offer precise vaccination recommendations and preventive measures for Japanese encephalitis. Travel clinics hold a crucial role in directing travelers and ensuring the provision of accurate and pertinent information to safeguard their well-being while journeying through JE-endemic areas [26]. The Advisory Committee on Immunization Practices (ACIP) generally advises vaccination for individuals who plan to spend a total of one month in areas where Japanese encephalitis (JE) is endemic during the transmission season. However, the length of the travel period is not the sole determinant for vaccination, as instances have been reported of JE cases among short-term travelers exposed unexpectedly for less than a week. JE is a rare yet potentially severe ailment, and vaccination can confer substantial protection. Travelers to Asia are recommended to receive the JE vaccine if their plans involve significant time spent outside major urban zones. Individuals considering return trips to Asia might also find vaccination beneficial when considering cumulative risk.

Travelers with stays of less than one month in endemic regions should ponder vaccination if their activities involve elevated exposure risk, such as agricultural work or outdoor sports, lodging in accommodations without screens, bed nets, or air conditioning, or if they intend to travel to outbreak-prone areas. Expatriates planning to reside in Asia for durations exceeding 6–12 months, even within urban locales, are strongly urged to undergo JE vaccination, given their frequent extensive travel throughout the region for both work and leisure. The JE vaccine available in the United States is Ixiaro (Valneva), an inactivated vaccine cultured in Vero cells. For children aged 2 months and above, the primary immunization entails two intramuscular doses administered on days 0 and 28, to be completed at least a week before departure. The dosage is 0.25 mL for children under 3 years and 0.5 mL for those aged 3 years and above. For adults with ongoing JE exposure, a booster dose is recommended 1–2 years post the primary course. Limited evidence currently supports the necessity of boosters for those under 18 years old. An accelerated vaccination schedule, involving doses on days 0 and 7, with a booster in a year, has demonstrated robust protection and is endorsed for last-minute travelers aged 18 to 65 years visiting high-risk areas and engaging in planned outdoor activities, accounting for seasonal risk factors [27].

5. Rabies Vaccines

Rabies constitutes an acute encephalitis that results from infection with the Rabies virus (RABV), a member of the Rhabdoviridae virus family. It leads to an estimated annual count of around 59,000 human fatalities, although this number might be an underestimate. Once clinical manifestations emerge, Rabies typically progresses to a fatal outcome. Its prevalence remains significant and underreported, particularly in regions with limited resources and economies, such as Asia and Africa. In these areas, restricted healthcare access and a low rate of domestic dog vaccinations contribute to the virus's spread. In the United States, while Rabies is less frequent, it is primarily transmitted by wild animals like bats, raccoons, skunks, and foxes. Domesticated cats and dogs also run the risk of contracting Rabies if not immunized. Additionally, larger carnivores like coyotes, bobcats, mountain lions, wolves, bears, woodchucks, and beavers should be treated as potentially rabid (unless proven otherwise) if they engage in unprovoked attacks on humans [28]. The Rabies vaccine is markedly efficacious and can avert approximately 99% of fatalities when administered promptly following exposure. There exist two principal strategies for Rabies prevention through vaccination: pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). PrEP involves the administration of the Rabies vaccine to individuals at potential risk of encountering the virus, such as veterinarians and animal handlers. Conversely, PEP entails administering the vaccine subsequent to a suspected Rabies exposure to avert the onset of the disease [29].

Rabies constitutes an acute and rapidly progressing encephalitis that stems from the Rabies virus (RABV), a single-stranded RNA virus classified within the family Rhabdoviridae and the genus Lyssavirus. The virus's primary mode of transmission is through the saliva of a rabid animal, typically via a bite. Nevertheless, it can also

be transmitted through contact with contaminated urine, sweat, and nervous tissues. It's noteworthy that RABV is not considered a bloodborne pathogen. Following a bite or exposure to a rabid animal, the virus travels from the wound into the peripheral nervous system, then migrates to the brain, where it reproduces. Subsequently, the virus disseminates through various tissues, including the salivary glands, thus initiating the transmission cycle. While rare instances of human-to-human transmission have been reported, these cases remain exceptional and are often associated with transmission from infected tissue or organ transplantation [30]. The significance of preventing Rabies cannot be overstated, and the timely administration of the Rabies vaccine subsequent to exposure can preclude the onset of the disease. Prompt medical attention and post-exposure prophylaxis are vital for individuals who have been bitten or exposed to potentially rabid animals, as this can impede the virus's progression to the central nervous system and the subsequent development of the fatal disease. The incubation period of Rabies generally spans from 1 to 3 months, although documented cases have shown this range to extend from weeks to over a year. It's rare for clinical Rabies to develop beyond one year from exposure. The hallmark signs and symptoms of Rabies encompass discomfort or abnormal sensations at the wound site, fever, paralysis, delirium, convulsions, and hydrophobia (fear of water). Once the infection becomes clinically evident, death is almost invariably impending within a span of 7 to 10 days. To counteract Rabies post-exposure, the administration of the Rabies vaccine and Rabies immunoglobulin (RIG) during the incubation period proves highly effective. Rabies vaccines trigger the immune system to generate Rabies virus neutralizing antibodies (VNAs), which typically remain active for several years. The development of detectable antibodies usually requires around 7 to 10 days.[31]

To effectively prevent Rabies after exposure, the Rabies vaccine and Rabies immunoglobulin (RIG) are potent interventions, especially when administered during the incubation period. The Rabies vaccine prompts the immune system to generate Rabies virus neutralizing antibodies (VNAs), which typically remain effective for several years. The development of detectable antibodies typically takes around 7 to 10 days. The initial live attenuated injectable Rabies vaccine was developed and tested in 1885 by Louis Pasteur and Emile Roux, utilizing rabbit nerve tissue. However, since 1984, the World Health Organization (WHO) has advised discontinuing the use of nerve tissue vaccines due to their potential for severe adverse events and reduced efficacy. Instead, contemporary concentrated, purified cell culture and embryonated egg-based Rabies vaccines (CCEEVs) are now recommended. In the United States, two types of CCEEVs are authorized for use: human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV) [32]. Both can be employed for pre- or post-exposure prophylaxis and are administered intramuscularly (IM). For post-exposure prophylaxis (PEP), two human Rabies immunoglobulins are available in the United States: HyperRabTM S/D and Imogam® Rabies-HT. These immunoglobulins are IgG preparations derived from human donor plasma and are formulated exclusively for IM administration. RIG confers passive immunity, providing protection until the actively acquired immunity from the Rabies vaccine becomes effective. It's crucial to promptly seek medical attention and receive appropriate Rabies prophylaxis after any potential exposure to Rabies, as the disease is nearly universally fatal once symptoms appear [33].

6. Cholera Vaccines

Cholera, a diarrheal disease, is initiated by the gram-negative bacillus Vibrio cholerae, particularly the serogroups O1 or O139, characterized by variants of the lipopolysaccharide O antigen. V. cholerae O1 can be categorized into classical and El Tor biotypes according to their phenotypic features. Furthermore, these strains can be subdivided into serotypes Inaba and Ogawa, based on antigenic traits of the lipopolysaccharide O antigen. Globally, the V. cholerae O1 El Tor biotype predominates as the cause of cholera, with the Ogawa serotype being the most prevalent. In 11 Asian nations, a smaller proportion of cholera cases are attributed to V. cholerae O139. Given the potential for underreporting in various countries, the precise count of cholera cases remains uncertain. Nevertheless, estimates suggest that approximately 5 to 7 million cholera cases arise annually worldwide, resulting in over 100,000 fatalities. Cholera remains a substantial public health challenge, particularly in regions lacking sufficient access to clean water, sanitation, and healthcare resources [34].

Cholera's main mode of transmission is through the consumption of contaminated food or water. The disease is instigated when individuals ingest a significant number of V. cholerae organisms, ranging from 108 to 1011 in those with regular gastric acidity and 104 to 106 in those with reduced gastric acidity (hypochlorhydria). Infected individuals can excrete as many as 1013 V. cholerae organisms daily in their feces, which can lead to rapid infection spread in a population if food or water sources are contaminated. Disease severity varies based on

individual immunity and other factors. Asymptomatic or mild cases are common among individuals in endemic areas with existing immunity. Nonimmune individuals, however, can experience disease ranging from moderate diarrhea to severe, copious diarrhea known as cholera gravis. This severe form can be life-threatening, leading to death within hours of onset. The gravity of cholera is influenced by factors like the amount of ingested organisms, the infecting V. cholerae biotype, preexisting immunity, blood group, and more. Untreated or poorly treated cholera during outbreaks can result in death rates as high as 20%–50%, escalating to 70%–100% in cholera gravis cases. Adequate rehydration therapy is vital in managing cholera, substantially reducing the associated mortality rate to below 1%. Prompt and effective rehydration can prevent severe dehydration and electrolyte imbalances caused by the disease. Furthermore, access to clean water, sanitation, and improved healthcare facilities are pivotal in controlling and preventing cholera outbreaks. Cholera is a low-risk concern for travelers, with an estimated incidence of 0.2 cases per 100,000 European and North American travelers. [35, 36, 37]

Despite the significant number of Americans (around 20 million) traveling to developing nations annually, only a small number (less than 20-30 cases) of cholera cases are reported among American travelers each year [38]. In Japan, regular microbiological screening of returning travelers with diarrhea reveals an incidence of cholera of 5 cases per 100,000 travelers for all destinations and 13 cases per 100,000 Japanese travelers to Indonesia, mainly Bali. During a recent cholera outbreak in Lima, Peru, a study of US embassy personnel with diarrhea found that 5 out of 317 US citizens were infected with V. cholerae. This indicates an estimated incidence of 5.3 cases per 1000 population per year or 44 cases per 100,000 population per month of exposure during the outbreak [36, 39]. Overall, the risk of developing cholera per month of stay in a developing country is estimated to be approximately 0.001%–0.01%, and cholera may present as traveler's diarrhea. Simple food and water precautions,[40] though often not strictly followed, can significantly reduce a traveler's risk of developing cholera. Cholera vaccines have been available for over 100 years and have been used with varying degrees of success in preventing the disease. [41, 42]

7. Meningococcal Vaccines

Neisseria meningitidis is a bacterium that can cause a wide range of clinical presentations, from asymptomatic carriage to severe and life-threatening meningitis. When it causes clinical disease, *N. meningitidis* is responsible for over 50% of meningitis cases, but it can also lead to other conditions such as pneumonia and bacteremia. The transmission of *N. meningitidis* occurs through close personal contact with respiratory secretions or saliva of infected individuals. Colonization of the bacteria is relatively common, and at any given time, around 5–10% of the population may carry the organism without showing symptoms[43].

In non-epidemic areas, invasive disease caused by *N. meningitidis* is rare, occurring at a rate of 0.5 to 10 cases per 100,000 individuals. However, in epidemic regions like the meningitis belt of Africa, the case rate can be drastically higher, reaching up to 1,000 cases per 100,000 individuals, particularly during peak seasons of outbreaks[44]. There are six major serogroups of *N. meningitidis* associated with human disease: A, B, C, X, Y, and W-135. These serogroups have different distributions and prevalence in various regions of the world. *N. meningitidis* is found worldwide, and its prevalence can vary with regional differences. Public health measures such as vaccination have been employed to control outbreaks and reduce the burden of the disease in affected regions [45].

Indeed, even though the prevalence of clinical disease caused by *N. meningitidis* is generally low in non-epidemic regions, the severity of meningococcal disease and the high mortality associated with *N. meningitidis* meningitis have prompted recommendations for vaccination of key populations. Vaccination is an important measure to prevent meningococcal disease and protect vulnerable individuals. In the United States, two types of meningococcal vaccines are currently available. One type provides protection against serogroups A, C, Y, and W-135, while the other vaccine specifically covers serogroup B. These vaccines are designed to stimulate the immune system to produce antibodies against the respective serogroups of *N. meningitidis*, offering protection against potential infection. Vaccination is typically recommended for individuals at increased risk of meningococcal disease, including: Adolescents and young adults: Meningococcal conjugate vaccines are recommended for routine vaccination in adolescents, with a booster dose recommended during the late teenage years or early adulthood. College students living in dormitories: College freshmen living in dormitory-style accommodations have a higher risk of meningococcal disease and are recommended to receive vaccination. Certain high-risk groups: People with certain medical conditions, such as immune deficiencies or functional asplenia (absence of a spleen), are at higher risk and are

advised to get vaccinated. Travelers to high-risk areas: Individuals traveling to regions where meningococcal disease is more prevalent, such as the meningitis belt of Africa, are encouraged to receive appropriate vaccination. Vaccination against *N. meningitidis* is an important public health strategy to prevent outbreaks and protect vulnerable populations from the potentially severe consequences of meningococcal disease.

For serogroups A, C, Y, and W-135, there are two similar vaccines available: MenACWY-D (Menactra) and MenACWY-CRM (Menveo). Both of these vaccines are conjugate vaccines, which means that the sugar part of the bacteria's capsule (the polysaccharide) is joined to a carrier protein to stimulate a stronger and more long-lasting immune response. The previously available quadrivalent polysaccharide vaccine (MPSV4, or Menomune) was discontinued in August 2017. The conjugate vaccines MenACWY-D and MenACWY-CRM are approved for use in individuals aged 9 months and older (MenACWY-D) or 2 years and older (MenACWY-CRM) up to the age of 55 years. However, most health authorities recommend off-label usage for individuals over the age of 55 since there is currently no approved vaccine specifically for this age group. Conjugate vaccines have several advantages over the older polysaccharide vaccines. The polysaccharide vaccines only include the sugar part of the bacteria's capsule as the antigen, while the conjugate vaccines attach the sugar to a carrier protein, resulting in a stronger and more effective immune response [46]. After vaccination with the quadrivalent conjugate vaccines, protective antibody levels against all four serogroups develop within 10–14 days, and the vaccines are estimated to provide around 90–95% protection. The duration of protection is shorter in children under 5 years of age but is generally considered to be 5 years in adolescents and adults. Conjugate vaccines elicit stronger immunologic memory, leading to recommended revaccination only every 5 years in adults. They also reduce the carriage of bacteria in the nasopharynx, interrupt transmission more effectively, and help establish population protection against the targeted serogroups. These factors make conjugate vaccines a preferred choice over the older polysaccharide vaccines for meningococcal disease prevention. (Table 1) [47].

Table 1: Two types of meningococcal vaccines are available in the U.S.

vaccine	Trade Name	Age Of Vaccine Initiation	Dose	Interval Since First Dose	Booster
Conjugate meningococcal A,C,W and Y vaccine	Menveo [48]	2 month 7-23 month ≥ 2 Years	0.5 ml 0.5 ml 0.5 ml	0, 2, 4, 10 montth 0, 3 month (2nd dose administered in 2nd year of life) 1 dose if traveling, then 2 dose given 8 weeks apart	If at continued risk
	Menactra [49]	9-23 month ≥ 2 Years	0.5 ml 0.5 ml	0, 3 month 1 dose	If at continued risk
Meningitis B vaccine	Trumenba [50]	10-25 Years	0.5 ml	0, 1-2, 6 month or 0,6 month The 3-dose schedule is preferred for groups at increased risk where more rapid protection is desired	None
	Bexsero [51]	10-25 Years	0.5 ml	0, ≥ 1 month	None

Conclusion

The evolution of vaccination stands as a significant achievement in public health over the last two centuries. Beginning with Edward Jenner's groundbreaking smallpox vaccine in 1796, a multitude of vaccines have since been developed and are currently in use within the realm of travel medicine. Simultaneously, many others are undergoing clinical trials or still in the developmental stage. The impetus behind vaccine innovation has been the burden and severity of diseases, matched with advances in microbiology and vaccine technology. To curtail the cross-border transmission of diseases, diverse public health entities, institutions, and organizations have devised policies stipulating vaccination requirements for travelers. These mandates can differ from country to country, hinging on factors like the rationale behind the requirement, the intended breadth of application, the specific target demographic, and the necessity for reinforcement. Numerous aspects can influence the formulation of vaccination policies and traveler requirements. These include the emergence or eradication of epidemics, substantial rates of morbidity and mortality,

the absence of effective treatments, implications for the tourism sector, and advancements in vaccine development. Furthermore, political and cultural factors, as well as the historical context of vaccine policies, have a central role in shaping the decisions undertaken by policymakers responsible for vaccine mandates. The ongoing COVID-19 pandemic has expedited the creation and implementation of novel vaccine platforms. The widespread adoption of COVID-19 vaccine verification is projected to profoundly influence vaccination policies for travelers in the future, thereby impacting practices and perspectives in this domain. As the situation continues to evolve, the stipulations for traveler vaccinations may undergo further transformations, reflecting the insights gained from the pandemic and the ongoing endeavors to ensure global health and safety.

Review Highlights

What Is Already Known?

Travel medicine has seen vaccine development progress, starting with Jenner's smallpox vaccine. Vaccines play a key role in curbing disease spread among travelers. Factors like disease severity, microbiology advances, and technology drive vaccine evolution. Public health policies shape vaccination requirements based on outbreaks, mortality rates, and preventive strategies. COVID-19 sped up vaccine development and verification for global travel. Future policies will learn from the pandemic, ensuring traveler well-being and safety.

What Does This Study Add?

This study delves into the history of travel vaccines and underscores their pivotal role in disease prevention. It also examines the abrupt impact of the COVID-19 pandemic on travel vaccine policies, showcasing how global health challenges are being addressed. This study adds value to the field of travel medicine, equipping healthcare providers, policymakers, and travelers with a deeper understanding of the crucial role of travel vaccines in promoting safe and secure global mobility.

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Conflict of Interest

The authors have no conflict of interest to declare.

References

1. Orenstein, W. A., & Ahmed, R. (2017). Simply put: Vaccination saves lives. Proceedings of the National Academy of Sciences, 114(16), 4031-4033. doi:https://doi.org/10.1073/pnas.1704507114.

2. Costa, M., Oberholzer-Riss, M., Hatz, C., Steffen, R., Puhan, M., & Schlagenhauf, P. (2015). Pre-travel health advice guidelines for humanitarian workers: a systematic review. Travel medicine and infectious disease, 13(6), 449-465. Doi: https://doi.org/ 10.1016/j.tmaid.2015.11.006.

3. Gautret, P., Angelo, K. M., Asgeirsson, H., Duvignaud, A., van Genderen, P. J., Bottieau, E., ... & Weber, R. (2019). International mass gatherings and travel-associated illness: A GeoSentinel cross-sectional, observational study. Travel medicine and infectious disease, 32, 101504. Doi:https://doi.org/10.1016/j.tmaid.2019.101504.

4. Weinberger, B., & Grubeck-Loebenstein, B. (2012). Vaccines for the elderly. Clinical Microbiology and Infection, 18, 100-108 Doi: https://doi.org/10.1111/j.1469-0691.2012.03944.x.

5. Simpson, K., Heymann, D., Brown, C. S., Edmunds, W. J., Elsgaard, J., Fine, P., ... & Wapling, A. (2020). Human monkeypox–After 40 years, an unintended consequence of smallpox eradication. Vaccine, 38(33), 5077-5081. Doi: https://doi.org/ 10.1016/j.vaccine.2020.04.062.

6. Saleh, A., Qamar, S., Tekin, A., Singh, R., & Kashyap, R. (2021). Vaccine development throughout history. Cureus, 13(7). Doi: https://doi.org/ 10.7759/cureus.16635.

7. Sánchez-Sampedro, L., Perdiguero, B., Mejías-Pérez, E., García-Arriaza, J., Di Pilato, M., & Esteban, M. (2015). The evolution of poxvirus vaccines. Viruses, 7(4), 1726-1803. Doi: https://doi.org/ 10.3390/v7041726 .

8. Beck, A. S., & Barrett, A. D. (2015). Current status and future prospects of yellow fever vaccines. Expert review of vaccines, 14(11), 1479-1492. Doi: https://doi.org/10.1586/14760584.2015.1083430.

9. Pavli, A., & Maltezou, H. C. (2021). COVID-19 vaccine passport for safe resumption of travel. Journal of Travel Medicine, 28(4), taab079. Doi: https://doi.org/10.1093/jtm/taab079.

10. Gaythorpe, K.A.; Hamlet, A.; Jean, K.; Ramos, D.G.; Cibrelus, L.; Garske, T.; Ferguson, N. The global burden of yellow fever. Elife 2021, 10, e64670. Doi: https://doi.org/10.7554/eLife.64670

11. World Health Organization. (2018). A global strategy to eliminate yellow fever epidemics (EYE) 2017–2026.

12. World Health Organization. (1955). Standards for the manufacture and control of yellow fever vaccine: annex I:

annex II: annex III (No. MH/CT/78.55). World Health Organization.

13. Theiler, M., & Smith, H. H. (1937). The effect of prolonged cultivation in vitro upon the pathogenicity of yellow fever virus. The Journal of experimental medicine, 65(6), 767-786. Doi: https://doi.org/ 10.1084/jem.65.6.767

14. Casey, C. G., Iskander, J. K., Roper, M. H., Mast, E. E., Wen, X. J., Török, T. J., ... & Mootrey, G. (2005). Adverse events associated with smallpox vaccination in the United States, January-October 2003. Jama, 294(21), 2734-2743. Doi: https://doi.org/ 10.1001/jama.294.21.2734.

15. Crotty, S., Felgner, P., Davies, H., Glidewell, J., Villarreal, L., & Ahmed, R. (2003). Cutting edge: long-term B cell memory in humans after smallpox vaccination. The Journal of Immunology, 171(10), 4969-4973. Doi: https://doi.org/ 10.4049/jimmunol.171.10.4969.

16. Monath, T. P., Caldwell, J. R., Mundt, W., Fusco, J., Johnson, C. S., Buller, M., ... & Weltzin, R. (2004). ACAM2000 clonal Vero cell culture vaccinia virus (New York City Board of Health strain)–a second-generation smallpox vaccine for biological defense. International journal of infectious diseases, 8, 31-44. Doi: https://doi.org/ 10.1016/j.ijid.2004.09.002.

17. Hall, R. N., King, T., O'Connor, T. W., Read, A. J., Vrankovic, S., Piper, M., & Strive, T. (2021). Passive Immunisation against RHDV2 Induces Protection against Disease but Not Infection. Vaccines, 9(10), 1197. Doi: https://doi.org/ 10.3390/vaccines9101197.

18. Helmick, M. J., Morrow, C. B., White, J. H., & Bordwine, P. (2023). Widespread Community Transmission of Hepatitis A Virus Following an Outbreak at a Local Restaurant—Virginia, September 2021–September 2022. Morbidity and Mortality Weekly Report, 72(14), 362. Doi: https://doi.org/ 10.15585/mmwr.mm7214a2.

19. Armstrong, M. E., Giesa, P. A., Davide, J. P., Redner, F., Waterbury, J. A., Rhoad, A. E., ... & Lewis, J. A. (1993). Development of the formalin-inactivated hepatitis A vaccine, VAQTATM from the live attenuated virus strain CR326F. Journal of hepatology, 18, S20-S26. Doi: https://doi.org/ 10.15585/mmwr.mm7214a2.

20. Xu, C., Zhang, W., Pan, Y., Wang, G., Yin, Q., Fu, S., ... & Wang, H. (2022). A bibliometric analysis of global research on Japanese encephalitis from 1934 to 2020. Frontiers in Cellular and Infection Microbiology, 12, 833701. Doi: https://doi.org/ 10.3389/fcimb.2022.833701.

21. Jacobsen, K. H. (2018). Globalization and the changing epidemiology of hepatitis A virus. Cold Spring Harbor Perspectives in Medicine, 8(10). Doi: https://doi.org/ 10.1101/cshperspect.a031716.

22. Duvoux, C., Belli, L. S., Fung, J., Angelico, M., Buti, M., Coilly, A., ... & Berenguer, M. (2021). 2020 position statement and recommendations of the European Liver and Intestine Transplantation Association (ELITA): management of hepatitis B virus-related infection before and after liver transplantation. Alimentary Pharmacology & Therapeutics, 54(5), 583-605. Doi: https://doi.org/ 10.1111/apt.16374.

23. Kumar, R. (2020). Understanding and managing acute encephalitis. F1000Research, 9. Doi: https://doi.org/10.12688/f1000research.20634.1.

24. McGuinness, S. L., Lau, C. L., & Leder, K. (2023). The evolving Japanese encephalitis situation in Australia and implications for travel medicine. Journal of Travel Medicine, 30(2), taad029. Doi: https://doi.org/ 10.1093/jtm/taad029.

25. Connor, B. A., Hamer, D. H., Kozarsky, P., Jong, E., Halstead, S. B., Keystone, J., ... & Bunn, W. B. (2019). Japanese encephalitis vaccine for travelers: risk-benefit reconsidered. Journal of Travel Medicine, 26(5), taz037. Doi: https://doi.org/ 10.1093/jtm/taz037.

26. Jelinek, T., Burchard, G. D., Dieckmann, S., Bühler, S., Paulke-Korinek, M., Nothdurft, H. D., ... & Pellegrini, M. (2015). Short-term immunogenicity and safety of an accelerated pre-exposure prophylaxis regimen with Japanese encephalitis vaccine in combination with a rabies vaccine: a phase III, multicenter, observer-blind study. Journal of travel medicine, 22(4), 225-231. Doi: https://doi.org/ 10.1111/jtm.12210.

27. Ericsson, C. D., Steffen, R., Shlim, D. R., Solomon, T., Ericsson, C. D., & Steffen, R. (2002). Japanese encephalitis vaccine for travelers: exploring the limits of risk. Clinical infectious diseases, 35(2), 183-188. Doi: https://doi.org/ 10.1086/341247

28. Hicks, D. J., Fooks, A. R., & Johnson, N. (2012). Developments in rabies vaccines. Clinical & Experimental Immunology, 169(3), 199-204. Doi: https://doi.org/10.1111/j.1365-2249.2012.04592.x.

29. Yang, D. K., Kim, H. H., Lee, K. W., & Song, J. Y. (2013). The present and future of rabies vaccine in animals. Clinical and Experimental Vaccine Research, 2(1), 19-25. Doi: https://doi.org/10.7774/cevr.2013.2.1.19.

30. World Health Organization. (2018). Rabies vaccines: WHO position paper, April 2018–Recommendations. Vaccine, 36(37), 5500-5503. Doi: https://doi.org/ 10.1016/j.vaccine.2018.06.061.

31. Gautret, P., & Parola, P. (2012). Rabies vaccination for international travelers. Vaccine, 30(2), 126-133. Doi: https://doi.org/ 10.1016/j.vaccine.2011.11.007.

32. Manning, S. E., Rupprecht, C. E., Fishbein, D., Hanlon, C. A., Lumlertdacha, B., Guerra, M., ... & Hull, H. F. (2008). Human rabies prevention—United States, 2008:

recommendations of the advisory committee on immunization practices. MMWR Recomm Rep, 57(RR-3), 1-28.

33. Yusibov, V., Hooper, D. C., Spitsin, S. V., Fleysh, N., Kean, R. B., Mikheeva, T., ... & Koprowski, H. (2002). Expression in plants and immunogenicity of plant virus-based experimental rabies vaccine. Vaccine, 20(25-26), 3155-3164. Doi: https://doi.org/ 10.1016/S0264-410X(02)00260-8.

34. Ramamurthy, T., Yamasaki, S., Takeda, Y., & Nair, G. B. (2003). Vibrio cholerae O139 Bengal: odyssey of a fortuitous variant. Microbes and infection, 5(4), 329-344. Doi: https://doi.org/ 10.1016/S1286-4579(03)00035-2.

35. Trolle, H., Forsberg, B., King, C., Akande, O., Ayres, S., Alfvén, T., & Elimian, K. (2023). A scoping review of facilitators and barriers influencing the implementation of surveillance and oral cholera vaccine interventions for cholera control in lower-and middle-income countries. BMC Public Health, 23(1), 455. Doi: https://doi.org/ 10.1186/s12889-023-15326-2

36. Wittlinger, F., Steffen, R., Watanabe, H., & Handszuh, H. (1995). Risk of cholera among Western and Japanese travelers. Journal of Travel Medicine, 2(3), 154-158. Doi: https://doi.org/ 10.1111/j.1708-8305.1995.tb00643.x.

37. Cabrera, A., Lepage, J. E., Sullivan, K. M., & Seed, S. M. (2017). Vaxchora: a single-dose oral cholera vaccine. Annals of Pharmacotherapy, 51(7), 584-589. Doi: https://doi.org/ 10.1177/1060028017698.

38. Centers for Disease Control and Prevention (CDC. (1999). Summary of notifiable diseases, United States, 1998. MMWR. Morbidity and mortality weekly report, 47(53), ii-92.

39. Norman, F. F., & Chen, L. H. (2023). Travel-associated melioidosis: a narrative review. Journal of Travel Medicine, 30(3), taad039. Doi: https://doi.org/ 10.1093/jtm/taad039

40. Taylor, D. N., Rizzo, J., Meza, R., Perez, J., & Watts, D. (1996). Cholera among Americans living in Peru. Clinical infectious diseases, 22(6), 1108-1109. Doi: https://doi.org/ 10.1093/clinids/22.6.1108.

41. Steffen, R., Rickenbach, M., Wilhelm, U., Helminger, A., & Schär, M. (1987). Health problems after travel to developing countries. Journal of Infectious Diseases, 156(1), 84-91. Doi: https://doi.org/ doi.org/10.1093/infdis/156.1.84.

42. Montero, D. A., Vidal, R. M., Velasco, J., George, S., Lucero, Y., Gómez, L. A., ... & O'Ryan, M. (2023). Vibrio cholerae, classification, pathogenesis, immune response, and trends in vaccine development. Frontiers in Medicine, 10, 1155751. Doi: https://doi.org/ 10.3389/fmed.2023.1155751.

43. Ali, A., Jafri, R. Z., Messonnier, N., Tevi-Benissan, C., Durrheim, D., Eskola, J., ... & Abramson, J. (2014). Global practices of meningococcal vaccine use and impact on invasive disease. Pathogens and Global Health, 108(1), 11-20. Doi: https://doi.org/ 10.1179/2047773214Y.0000000126.

44. Wilder-Smith, A. (2008). Meningococcal disease: risk for international travellers and vaccine strategies. Travel Medicine and Infectious Disease, 6(4), 182-186. Doi: https://doi.org/10.1016/j.tmaid.2007.10.002.

45. Cramer, J. P., & Wilder-Smith, A. (2012). Meningococcal disease in travelers: update on vaccine options. Current opinion in infectious diseases, 25(5), 507-517. Doi: https://doi.org/ 10.1097/QCO.0b013e3283574c06.

46. Masaquel, C., Schley, K., Wright, K., Mauskopf, J., Parrish, R. A., Presa, J. V., & Hewlett Jr, D. (2023). The Impact of Social Determinants of Health on Meningococcal Vaccination Awareness, Delivery, and Coverage in Adolescents and Young Adults in the United States: A Systematic Review. Vaccines, 11(2), 256. Doi: https://doi.org/ 10.3390/vaccines11020256.

47. Soeters, H. M., McNamara, L. A., Blain, A. E., Whaley, M., MacNeil, J. R., Hariri, S., & Mbaeyi, S. A. (2019). University-based outbreaks of meningococcal disease caused by serogroup B, United States, 2013–2018. Emerging infectious diseases, 25(3), 434. Doi: https://doi.org/10.3201/eid2503.181574.

48. Lee, G. M. (2020). Preventing infections in children and adults with asplenia. Hematology 2014, the American Society of Hematology Education Program Book, 2020(1), 328-335. Doi: https://doi.org/ 10.1182/hematology.2020000117.

49. Myers, T. R., McNeil, M. M., Ng, C. S., Li, R., Marquez, P. L., Moro, P. L., ... & Cano, M. V. (2020). Adverse events following quadrivalent meningococcal diphtheria toxoid conjugate vaccine (Menactra®) reported to the Vaccine Adverse Event Reporting System (VAERS), 2005–2016. Vaccine, 38(40), 6291-6298. Doi: https://doi.org/ 10.1016/j.vaccine.2020.07.039.

50. Patton, M. E., Stephens, D., Moore, K., & MacNeil, J. R. (2017). Updated recommendations for use of MenB-FHbp serogroup B meningococcal vaccine—Advisory Committee on Immunization Practices, 2016. Morbidity and Mortality Weekly Report, 66(19), 509. Doi: https://doi.org/ 10.15585/mmwr.mm6619a6.

51. Perez-Vilar, S., Dores, G. M., Marquez, P. L., Ng, C. S., Cano, M. V., Rastogi, A., ... & Duffy, J. (2022). Safety surveillance of meningococcal group B vaccine (Bexsero®), Vaccine Adverse Event Reporting System, 2015–2018. Vaccine, 40(2), 247-254. Doi: https://doi.org/ 10.1016/j.vaccine.2021.11.071.