UNIT NO. 3

MENINGOCOCCAL AND TRAVELLERS' VACCINATIONS

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ABSTRACT

The increase in international tourism has created demand for vaccination to protect against travel-associated illness. The decision to vaccinate travellers involves risk-benefit assessment. Most currently used travel vaccines include the meningococcal vaccine, yellow fever vaccine, typhoid vaccine, and Japanese encephalitis vaccine.

This review addresses the limitations posed by the meningococcal polysaccharide vaccine, the different quadrivalent meningococcal conjugate vaccines available, the current recommendations in children and adults and the development of new meningococcal B vaccines.

This review also addresses the current recommendations for yellow fever vaccines, new typhoid conjugate vaccines, changing epidemiology of Japanese encephalitis (JE), and new recommendations for the JE vaccines.

Keywords: A Risk-benefit Assessment; Immunologic Memory; Conjugate Vaccine; Cell Culture-based;

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INTRODUCTION

International tourist arrivals reached 1,235 million in 2016, a growth of 46 million or 4 percent over 2015.[1] The strongest growth was recorded in Africa and Asia-Pacific regions. Primary care and travel medicine physicians are likely to be consulted by international travellers with respect to required and recommended vaccines and adequate protection to avoid travel-associated illness.

The decision to vaccinate a traveller involves a risk-benefit assessment based on the risk of disease, the benefits of vaccination, the individual's underlying health, the cost of the vaccine and the risk of adverse events associated with the vaccine.

MENINGOCOCCAL VACCINES

Globally, six serogroups (A, B, C, W-135, X, and Y) account for over 90 percent of invasive meningococcal disease (IMD).[2] Group A is the most common capsular group, particularly in Sub-Saharan Africa. Group B is endemic in high- and middle-income countries. Thus WHO estimates approximately 500,000 cases of IMD occur annually worldwide, resulting in over 50,000 deaths.[3] Meningococcus is carried in the nasopharynx, and IMD results following invasion of the blood or meninges by a hypervirulent strain.[4]

There are 2 types of meningococcal vaccines available in Singapore (Table 1):

1. Meningococcal polysaccharide vaccine (MPV) — quadrivalent (A, C, W-135, and Y)
   Menomune — Sanofi Pasteur discontinued production in mid-2017
   Mencevax — GlaxoSmith Kline discontinued production in June 2016

   Other limitations of MPV include short-lived protection (3–5 years), lack of immunologic memory, negligible impact on nasopharyngeal carriage, and presence of hyporesponsiveness after repeated doses.[5]

2. Meningococcal conjugate vaccine (MCV) — available as quadrivalent A, C, W-135 and Y.

   Conjugate polysaccharide vaccines have been developed in which polysaccharide capsules are conjugated to a carrier protein to induce a T-cell-dependent response, making these vaccines immunogenic from early infancy and giving a stronger anamnestic response (i.e. immunologic memory) at re-exposure.[6]

MenACWY-DT (Menactra , Sanofi Pasteur) was approved as a 2-dose series for children aged 9–23 months and as a single dose for persons aged 2–55 years. In 2006, the correlation between GBS and MenACWY-DT was studied after the reporting of 17 cases of GBS following MenACYW-DT vaccination.[7] The risk of GBS was estimated to be 0.4–1.3 per million doses. 2010 ACIP has removed a history of GBS as a precaution of Menactra.

MenACYW-CRM (Menveo,GSK). In 2013 ACIP extended recommendation to include children 2-23 months in addition to 2-55 year individuals. A comparative trial in adults showed that both MenACWY-DT and MenACYW-CRM induced immune responses to all 4 serogroups with post-vaccination titres being higher for MenACYW-CRM. A 2011 study showed that healthy adults who received MenACYW-CRM had more robust immune responses to all 4 serogroups as compared to subjects who received either MenACWY-DT or MPV-4.[11] It has been approved for use in persons aged 2 years and above in Europe and Singapore.

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MenACWY-TT (Nimenrix, GSK) was the first meningococcal quadrivalent conjugate vaccine to be approved in Europe in 2012. It was approved as 3 doses for children 6–12 weeks and as a single dose for persons aged 1 year and older.[10] Dbaibo et al demonstrated that a single-dose MenACWY-TT given to healthy adults ≥56 years of age induced a vaccinees response ≥ 76 percent with ≥93 percent of vaccinees achieving SBA (rSBA) titres ≥ 1:128 against all 4 serogroups.[9]

Recommendations for Use of Meningoccocal Vaccines:[12]

a. Children and adults who have persistent complement deficiencies or functional or anatomic asplenia.

b. Persons who are first-year college students living in residential housing.

c. Persons travelling to or resident in countries where meningococcal disease is hyper-endemic or epidemic. Vaccination against meningococcal disease is a pre-requisite for Hajj/Umrah pilgrims to Saudi Arabia. The meningococcal vaccine is recommended for travellers to the African meningococcal belt particularly during the dry season (December to June).

d. Microbiologists routinely exposed to isolates of *Neisseria meningitidis.*

Meningococcal B Vaccines

Two Meningococcal B vaccines have been licensed by the Food and Drug Administrations (FDA) for use in the United States (Table 2).

MenB-FHbp (Trumenba; Pfizer) was licensed in the US in 2014. It is a bivalent vaccine consisting of 2 different recombinant lipidated factor H binding protein (Fhbp) antigens, one from FHbp subfamily A and one from FHbp subfamily B.

MenB-4C (Bexsero, Novartis) was licensed in the US in 2015. It is a multicomponent vaccine consisting of 3 recombinant proteins from *N meningitidis* [FHbp neisserial adhesion A (NadA)], factor H binding protein (FHbp) and neisserial heparin-binding antigen protein (NHBA) and outer membrane vesicles containing PorA PI.4 (New Zealand epidemic strain N298/254).

Both vaccines are currently recommended for persons aged 10–25 years of age, who are at increased risk of Meningococcal serogroup B infection, including those with persistent complement component deficiencies, anatomic or functional asplenia, and people living in an outbreak area.[13] The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses.

YELLOW FEVER VACCINE

Yellow Fever (YF) is an acute viral haemorrhagic disease caused by an arbovirus of flavivirus genus. The YF virus is transmitted to human beings through the bites of infected mosquitoes of the Aedes and Hemogogus genera. Worldwide, ~ 200,000 cases of YF occur annually with a case fatality rate of ~15 percent.[14] Forty-five endemic countries are at risk of YF in Africa and Latin America.

From December 2015 until end 2016, YF caused a large outbreak in Angola and the Democratic Republic of Congo (DRC).[15] From December 2016, a new YF outbreak developed in Brazil that resulted in 723 confirmed cases and 237 deaths.[16]

The number of YF cases has increased over the past 2 decades due to declining population immunity to infection, deforestation, urbanisation, population movements and climate change. There is no approved antiviral for YF and therefore treatment is supportive.

Types of YF Vaccines and Recommendations

Vaccination is the single most important measure for preventing YF. YF vaccines have been available for more than 60 years. Two 17D substrain vaccines are being manufactured, namely 17DD and 17D-204YF vaccines. The 17DD YF vaccines are manufactured in Brazil and are used in Brazil and many other South American countries. The 17D-204 YF vaccine is a freeze-dried, live attenuated, highly effective vaccine. It is available worldwide in single or multi-dose vials and should be stored at 4–8°C. The 0.5ml dose is injected subcutaneously. It provides effective immunity within one week for 95 percent of vaccinees.[17]

Recommendations for YF Vaccine: Persons aged ≥9 months of age who are travelling or living in areas with risk of YF virus transmission.[18]

Decisions regarding the use of YF vaccine for travellers must take into account the overall risk for travel-associated YF disease, the high mortality when it occurs, vaccine requirements for International Health Regulations, contraindication or precautions for vaccination, and risk of adverse events following YF vaccine administration.

The World Health Organization's Strategic Advisory Group of Experts in Immunizations (SAGE) concluded in April 2013 that a single dose of YF vaccine is sufficient to confer sustained immunity and lifelong protection against YF disease and a booster dose of vaccine is not needed.[19] In May 2014, the World Health Assembly adopted the recommendation to remove the 10-year booster dose requirement from the International Health Regulations by June 2016.[20]

However, additional doses of YF vaccine are recommended for certain populations (i.e. pregnant women, stem-cell transplant recipients and HIV-infected persons). Certain travellers travelling for prolonged periods in an endemic area and

laboratory workers who handle wild-type YF viruses are also recommended to receive additional doses of YF vaccine.[21]

YF Vaccine Safety

The most common systemic side effects after YF vaccination include headache, asthenia, myalgia, malaise, fever, rash, and chills.

Serious adverse events related to YF vaccination include YF vaccine-associated viscerotropic disease (0.09 to 0.4 cases per 100,000 doses in population not exposed to the virus), neurologic or neuropathic disease (frequency of 0.8 cases per 100,000 doses), and severe hypersensitive reactions (<1 per million principally in persons with known egg sensitivity).

TYPHOID VACCINE

Typhoid fever is a serious, systemic infection caused by *Salmonella enterica* serotype Typhi. It results in nearly 2.2 million cases and 216,500 deaths annually, primarily in South Asia and Sub-Saharan Africa.[22] It is transmitted by the oral-faecal route, with most cases and deaths occurring in populations that lack access to safe drinking water and adequate sanitation and hygiene.

Paratyphoid fever, caused primarily by *Salmonella enterica* serotype Paratyphi A, Paratyphi B, and Paratyphi C, is an illness similar to typhoid fever. Serotype Paratyphi A is responsible for a growing proportion of enteric fever cases in many countries.[24]

Resistance to available antibiotics is common, and the prevalence of resistance is increasing.[23] Humans are the only reservoir for Typhi and a long-term carrier state occurs.

Currently, two safe and effective typhoid vaccines are available:

a. An injectable Vi capsular polysaccharide vaccine based on purified Typhi Vi antigen. (ViCPS vaccine; Typhim Vi, Sanofi Pasteur) for persons aged ≥2 years; given intramuscular 0.5 ml as a single dose. Revaccination is recommended every 3 years if continued exposure is expected.

b. A live attenuated oral Ty21a vaccine (Vivotif) available in capsule formulation for persons aged ≥2 years. The capsules must be kept refrigerated. It is registered as a 4-dose schedule in the US, taken on alternate days (day 0, 2, 4 and 6) and as a 3-dose schedule in Singapore (day 0, 2 and 4). All doses should be completed 1 week before potential exposure. Revaccination every 5 years is recommended.

A systematic review and meta-analysis revealed an estimated 2.5–3.0 year cumulative efficacy 55 percent (95% confidence interval, CI=30-70%) for Vi polysaccharide vaccine and 48 percent (CI=35–58%) for oral Ty21a vaccine, each based on a single trial[24]. In a trial in Kolkata, India, Vi polysaccharide vaccines had a protective effectiveness of 61 percent (CI=41–75%) among all participants (adults and children) and effectiveness of 80 percent (CI 53–91%) among children 2–4 years, probably due to herd effects.[25] A similar trial in Karachi, Pakistan, showed no protection among children aged 2–4 years.[26]

Ty21a vaccine should not be given until at least 3 days after the last dose of antimicrobial agent. Live attenuated Ty21a vaccine should not be used by immune-compromised persons. Ty21a vaccine can be administered simultaneously or at any interval before or after other live vaccines or immune globulin if indicated.

Newer-generation typhoid conjugate vaccines (TCVs) are under development. TCVs are expected to be immunogenic in children aged <2 years, to provide a booster effect (currently lacking for ViCPS vaccine) and a longer duration of protection.

On 3 January 2018, WHO prequalified the first conjugate vaccine called Typbar-TCV® developed by Bharat Biotech.[27] A "human challenge trial" to evaluate efficacy of Vi-Tetanus toxoid conjugate vaccine (Typbar-TCV, Bharat Biotech) in Oxford, England, showed an estimated efficacy of 87 percent in preventing typhoid fever.[28]

Limited observational data suggest that the oral Ty21a vaccine might offer some protection against Paratyphoid B.[29]

The typhoid vaccine is therefore recommended for:[30]

- Travellers to areas where there is a risk for exposure to Salmonella serotype Typhi;
- Persons with intimate exposure to documented Salmonella serotype Typhi chronic carriers; and
- Microbiologists and other laboratory workers routinely exposed to cultures of Salmonella serotype Typhi.

JAPANESE ENCEPHALITIS VACCINE

The Japanese Encephalitis (JE) virus is the most common cause of vaccine-preventable encephalitis in Asia and a large part of Western Pacific, including northern portions of Australia. The JE virus is a flavivirus transmitted by Culex mosquitoes. Wading birds, especially herons, serve as reservoirs for the JE virus, and pigs serve as amplifying hosts. Transmission occurs in areas such as pig farms and rice fields. Recently, infections have been documented more commonly in suburban regions, particularly in South Korea, China, Singapore, and Taiwan.[31, 32]

According to the WHO, annually there are about 67,900 global cases of JE, of which 20–30 percent are fatal and 30–50 percent of survivors have significant neurological sequelae.[33]

Recommendations for the use of JE vaccine:[34]

- For travellers who plan to spend one month or more in endemic areas during the JE virus transmission seasons. This includes long-term or recurrent travellers or expatriates based in urban areas who are likely to visit agricultural or rural areas.

- For short-term travellers (<1 month) to endemic areas during the transmission season who plan outdoor activities in rural or agricultural areas and those staying in accommodations without air-conditioning, screens, or bed nets. It should also be considered for travellers to an area with an ongoing outbreak.

Types of JE Vaccines

1. Inactivated mouse-derived vaccines (JE-MB)
   First generation vaccines were made from either the Nakayama or Beijing-1 virus strain. Limitations included uncertainty over duration of protection, requirement of multiple booster doses, and rare reports of acute disseminated encephalomyelitis temporarily associated with this type of vaccine.

2. Inactivated Vero cell-culture vaccines (JEspect, IXIARO, JEEV).

3. Cell-culture derived (primary hamster kidney) live attenuated vaccines based on SA-14-14-2 strain of JEV (CD.JEVAX) manufactured in China.

4. Live attenuated chimeric virus vaccine using the 17D-204 YF vaccine virus by replacing prM and E genes of YFV with that of an attenuated SA 14-14-2 strain of JEV (IMOJEV, ChimeriVax-JE).

The JE-MB vaccine is now commonly replaced by cell culture-based JE vaccines. The two new-generation JE vaccines currently available in Singapore are IMOJEV and IXIARO (Table 3). Available data do not raise concerns for those previously vaccinated with mouse-derived vaccines subsequently receiving any of the newer JE vaccines.[36]

SUMMARY

Vaccines are highly effective in protecting travellers against many infectious diseases. Vaccination is a key intervention in travel medicine. Several important new vaccines are in development, including meningococcal group B vaccines, typhoid conjugate vaccines, and Japanese Encephalitis vaccines.

The World Health Organization, the United States' Centers for Disease Control and Prevention, and the Health Protection Agency in the United Kingdom publish guidance for travel-health providers. Travel-medicine providers should ensure that they are up to date with the latest vaccine developments.

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LEARNING POINTS

- **Conjugate vaccines induce a T-cell-dependent response, making these vaccines more immunogenic and with a stronger immunologic memory at a re-exposure.**
- **Yellow fever vaccine is a live attenuated highly effective vaccine. WHO has recommended the removal of the 10-year booster dose requirement from the International Health Regulations by 2016.**
- **Two new-generation JE vaccines, IMOJEV and IXIARO, have replaced the first-generation inactivated mouse-derived JE vaccine (JE-MB).**

Table 1 : Quadrivalent Meningococcal Vaccine Registered for Use in Singapore

Type of Vaccine	Manufacturer	Age Group	Dose / schedule	Booster
Meningococcal ACWY polysaccharide Vaccine (MPV4) (Menomune)	Sanofi Pasteur	≥2 years	1 dose (1 dose = s/c 0.5ml)	Booster at 5y
MenACWY-DT (Menactra)	Sanofi Pasteur	9–22 months 2–55 years	2 doses 8 weeks apart 1 dose (1 dose = i/m 0.5mls)	a) Children's last dose <7years booster after 3years and repeated every 5years thereafter b) Persons last dose ≥7years; booster after 5years and every 5years thereafter
MenACWY-CRM (Menveo)	GlaxoSmith Kline	2–12months 7–23months ≥2	4 doses 0, 2, 4, 10-18mths 0, 3 mo 1 dose (1 dose=i/m 0.5ml)	As above
MenACWY-TT (Nimenmix)	Pfizer	6wk–12mths ≥12 months	3 doses 1st 2 doses 2mo apart 3rd dose – 12 mo of age Single dose (1 dose = i/m 0.5mls)	As above

Table 2 : Meningococcal B Vaccines

Type of Vaccine	Manufacturer	Age Group	Dose schedule	Booster
Meningococcal B (MenB-FHbp)	Pfizer	10–25y	a) 3 dose 0, 1–2mo, 6mo (persons at increased risk for meningococcal disease) b) 2 dose: 0, 6mos (for healthy adolescents not at increased risk for meningococcal disease) (1 dose – i/m 0.5ml	None
Meningococcal B (MenB-4C) (Bexsero)	GlaxoSmithKline	24mo–10y >10–25y	2 doses 2 doses 4mths apart (1 dose – i/m 0,5ml)	None

Table 3: Cell Culture-based JE vaccines

JE Vaccine	Age	Dose	Primary Series	Booster
Ixiaro	2 months to < 3y ≥3 yrs	i/m 0.25ml i/m 0.5ml	2 doses 28 days apart 2 doses 28 days apart	No data Individual ≥ 17 years who received primary doses >1 year previously, should be given booster dose if ongoing exposure to JEV
IMOJEV (Sanofi Pasteur)	≥9mo to <18y ≥18y	s/c 0.5mls s/c 0.5mls	single dose single dose	12–24 months after primary dose not required