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Vaccination against Mosquito Borne Viral Infections: Current Status

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ABSTRACT

Mosquito borne infectious diseases are among important group of diseases worldwide. Vaccination is available for some tropical mosquito-borne diseases, especially for Japanese encephalitis virus infection and yellow fever. There are also several attempts to develop new vaccines for the other mosquito-borne diseases such as malaria, dengue infection and West Nile virus infection. In this article, the author reviews the issues on vaccination of some important tropical mosquito borne infectious diseases.

Keywords: Mosquito, Vaccination, Japanese Encephalitis

INTRODUCTION

In preventive medicine, one considers three levels of primary, secondary and tertiary prevention (1). In primary prevention, we focus on the prevention of the unwanted event as soon as it is noticed. The primary prevention may include the control of vector, immunization, as well as chemoprophylaxis. In secondary prevention, early detection and prompt treatment is the main focus. Asymptomatic persons who have already developed risk factors or preclinical infectious diseases are identified and treated in this step. The efficiency of preventive treatments should lead us to the final goal of zero infections (2). In tertiary prevention, attention is paid to the control of disability or events sequel to the infection, including physical, psychological as well as social problems.

Vaccination is available for some tropical mosquito-borne diseases, especially for Japanese encephalitis virus infection and yellow fever. There are also several attempts to develop new vaccines for the other mosquito-borne diseases such as malaria, dengue infection and West Nile virus infection. In this article, the issues on vaccination of some important tropical mosquito borne infectious diseases are discussed.

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YELLOW FEVER

Yellow fever is a mosquito-borne infection. It is an infectious and non-contagious disease caused by an arbovirus, the yellow fever virus (3). The agent is maintained in jungle cycles among primates as vertebrate hosts and mosquitoes. It is transmitted in a cycle involving monkeys and mosquitoes, but human beings can also serve as the viremic host for mosquitos (1, 4). Recently Gubler noted that yellow fever was an old disease, having caused major epidemics in centuries past (5). Today the disease still affects as many as 200,000 persons annually in tropical regions of Africa and South America, and poses a significant hazard to unvaccinated travelers to these areas (4). Approximately 90% of the infections are mild or asymptomatic, while 10% result in severe clinical pictures with 50% fatality rate (4). Recent increases in the density and distribution of the urban mosquito vector, *Aedes aegypti*, as well as the rise in air travel increase the risk of introduction and spread of yellow fever to North and Central America, the Caribbean and Asia (4). Therefore, prevention of possible infection due to traveling is necessary.

Yellow fever is an arthropod-borne disease with symptoms ranging from mild fever to acute hepatonephritis, hemorrhages and often fatal shock (6, 7). The classical infection includes an incubation period of 3 – 6 days without prodomal symptoms (6). The symptomatic flu like illness is then developed. The period of infection is about 3 – 4 days (6). Typically, symptoms begin with fever, violent headache, malaise, chills, anoreixa, nausea, vomiting and lumbosacral myalgia (6). Luckily, most cases will turn into remission and abortive phases within 1 – 2 days (6). About 15 % of infected cases develop a period of intoxication, usually presented with several complications including a hemorrhagic episode, liver failure, and renal failure which subsequently leads to fatal conditions (6). Digoutte noted that mortality rate was high for hemorrhagic fever with hepatitis, reaching a 36% level (8). He also noted that the virulence of the yellow fever virus, as well as mortality in its wild and intermediate cycles, was much lower than the urban cycle (8).

Unlike other viral mosquito-borne diseases, an effective vaccine for yellow fever has been developed for years. 17D yellow fever vaccine is a well-known vaccine. Lyophilized vaccine without stabilizers deteriorates rapidly when exposed to temperatures above -20° C (9). WHO recommends that each lot of vaccine should meet the following stability tests: maintenance of potency (> 1,000 mouse i.c.LD50/human dose) with mean loss of titre < 1.0 log10 after being held at 37° C for 14 days (9). This vaccine is proved effective for control of yellow fever. Tomori proposed that over a ten-year period of stage-by-stage mass yellow fever vaccination campaigns integrated with successful routine immunisation, Africa could bring yellow fever under control (10). Tomori also noted that, for yellow fever to cease being a public health problem, Africa should maintain at least an annual 80% yellow fever vaccine coverage of children under the age of 1 year, and sustain a reliable disease surveillance system with a responsive disease control program (10). Tomori also suggested that this could be achieved at an affordable annual expenditure of less than US$ 1.00 per person per year, with a reordering of priorities (10).

Generally, yellow fever vaccine is a live attenuated vaccine. The recommended dosage is one dose of 0.5 ml subcutaneously. It is recommended as an inclusion in routine immunization with measles vaccine at nine months of age in endemic areas (11). Van Laethem argues that yellow fever vaccine is the only mandatory vaccine for certain African or South American countries (11). International health regulations require a

booster every 10 years (11). It is noted that this vaccine should not be given before six months of age and should be avoided during pregnancy (11). In addition, the vaccination is also recommended before traveling to those endemic countries (10). This vaccination remains important in travel medicine (12). The guidelines of the World Health Organization call for immunization against yellow fever at least 10 days before travel to endemic areas (one dose of 0.5 ml subcutaneously) (13). A yellow fever vaccination certificate is now the only vaccination certificate that should be required in international travel, and then only for a limited number of persons (11). Many countries require a valid international certificate of vaccination from travelers, including those in transit, arriving from infected areas or from countries with infected areas (11). Some countries require a certificate from all entering travelers, even those arriving from countries where there is no risk of yellow fever (11). However, Potasman et al found that the World Health Organization guidelines for yellow fever vaccination were frequently not followed (14). They noted that an initiative to explain to the public the importance of vaccination well before travel to endemic areas should be undertaken (14).

As previously mentioned, the vaccination is recommended to be used with special precautions in pregnancy. The risk of exposure to disease must be weighed against the potential risk of the vaccine during pregnancy (11). Cavalcanti et al reported that there was no indication that immunization with yellow fever vaccine in early pregnancy increases the risk of major malformations (15). However, an association was found between yellow fever vaccination during pregnancy and minor dysmorphisms, especially pigmented naevus (15).The vaccine is also contraindicated in immune-deficient patients and in individuals allergic to eggs (11). Vaccination for individuals with symptomatic HIV infection is still a controversy. In 2004, Kemper et al noted that HIV-infected patients should be more aware of the necessity for medical counsel prior to travel (16). Receveur et al reported that yellow fever vaccine 17D was effective and safe in 2 human immunodeficiency virus-infected patients without severe immunosuppression, one of whom traveled to Kenya and the other traveled to Senegal (17). Moss et al noted that the risk of serious complications attributable to yellow fever vaccine in HIV-infected persons had not been determined (18). In 2004, Tattevin et al concluded that yellow fever vaccine was safe and effective in HIV-infected patients (19). In addition, Leder et al noted that the use of yellow fever vaccine in the elderly should include special precautions since increased toxic effects following yellow fever vaccination in the elderly had recently been reported (20) In elderly persons, 17D vaccine is associated with a higher frequency of significant adverse effects and a lower incidence of common minor side-effects (21). In addition, the neutralizing antibody response is not diminished in healthy, elderly persons (21).

Concerning the adverse effects of yellow fever vaccination, fever is the most common side effect. According to the study of Osinusi et al, fever occurred in 12 (15.6%) children within 48 hours of vaccination, while it occurred in only 10 (12.9%) children within ten days of vaccination (22). An interesting rare complication of yellow fever vaccination is acute viscerotropic disease (23). This was reported to be related to 17D204 vaccine (23). Very rare cases of serious complications, including death, have recently been reported. Chan et al reported that severe, rapidly progressive, and ultimately fatal disease could follow the use of the 17D204 vaccine strain (24). In 2001, Martin et al reported three patients who developed severe illnesses days after yellow fever vaccination (25). The clinical presentations were characterized by fever, myalgia, headache, and confusion, followed by severe multisystemic illnesses (25). These 3 pa-

tients died and vaccine-related variants of yellow fever virus were found in plasma and cerebrospinal fluid of one of the vaccinated individuals (25). In addition, the convalescent serum samples of two vaccinated individuals showed antibody responses of at least 1:10240. Also, the immunohistochemical assay of the liver tissue showed yellow fever antigen in the Kuppfer cells. (25). Martin et al concluded that the clinical features, the temporal association with vaccination, the recovery of vaccine-related virus, the antibody responses, and the immunohistochemical assay collectively suggested a possible causal relation between the illnesses and yellow fever vaccination (25). Martin et al also noted that advanced age might be a risk factor for the illness temporally associated with yellow fever vaccination (25). In 2004, Lawrence et al noted that severe systemic adverse events following yellow fever vaccination had raised concern about the safety of YF vaccine, particularly among older people (26). They investigated the age-related rates of adverse events following YF vaccination reported to the Australian Adverse Drug Reactions Advisory Committee for the period 1993 to 2002 and found that the higher reported rates were detected among older people (26). Although there are reports on the adverse effects of yellow fever vaccination, the risk to unimmunized individuals either living in or travelling to areas where there is known yellow fever transmission is far greater than the risk of having a vaccine-related adverse event (18). Barrett et al noted that there was an unanimous agreement that the current 17D yellow fever vaccines have a highly favourable benefit-risk profile when used in persons at risk of exposure to the yellow fever virus, and that appropriate use of 17D yellow fever vaccines would minimize the occurrence of serious post-vaccination adverse effects (27). Martins et al proposed that activation/modulation of adaptive immunity, emerged simultaneously after 17D yellow fever first-time vaccination, was the key to prevent severe adverse reactions following immunization (28).

JAPANESE ENCEPHALITIS

Japanese encephalitis is another mosquito-borne infection. It is an infectious and non-contagious disease caused by an arbovirus, Japanese encephalitis (JE) virus (29, 30). In recent years there has been a dramatic resurgence or emergence of epidemic arboviral diseases in animals and humans (31, 32). Globally, JE virus is the most important emerging viral encephalitis. Recent work suggests that JE virus originated in the Indonesia-Malaysia region and has spread from there (33). Japanese encephalitis is a mosquito borne infection endemic over a wide area of Asia, and the south eastern parts of Russian Countries (34). This disease is the most important cause of epidemic encephalitis worldwide with 40,000 - 50,000 cases per year (35). The distribution of the vector for Japanese encephalitis was primarily limited to Asia. However, at present the geographical distribution of this disease is worldwide (29, 35). Similar to many tropical mosquito-borne diseases, recent increases in the density and distribution of the mosquito vector as well as the rise in air travel have increased the risk of introduction and spread of Japanese encephalitis to Western hemisphere (29). In Western hemisphere, Japanese encephalitis has just been diagnosed in travelers returning from endemic areas in the past few years (36).
Japanese encephalitis is associated with severe encephalitis, a high death rate and a high incidence of neurological sequelae in survivors (35). The diagnosis of Japanese encephalitis can be confirmed by serology, virus isolation, and molecular diagnosis (29).

The disease often appears in summer and typically affects 2 to 7-year-old children (37). Patients usually have a history of mosquito exposure in an endemic area. The incubation period ranges from three days to two weeks followed by a prodrome of flu like symptoms for several days. The occasional symptomatic child typically presents with a neurological syndrome characterized by altered sensorium, seizures, and features of intracranial hypertension (38). Alteration of consciousness and seizure can be seen. Kaur et al noted that the disease became an epidemic during the peak monsoon months of July and August and the fatality rate was 42.11% (39).

Similar to Yellow fever, an effective vaccine for Japanese encephalitis has been developed for years. A safe efficacious formalin-inactivated vaccine against Japanese encephalitis has been available for many years. Kabilan mentions that due to the limitations of vector control methods in Japanese encephalitis owing to sustainability and cost effectiveness of the programs, the feasibility of vaccination in endemic areas has to be considered as a preventive measure. For this purpose, identification of risk areas and target populations to be immunized, together with cost-evaluation of immunization should be emphasized (40). This vaccine is proved to be effective for the control of Japanese encephalitis, but is expensive. A newer live attenuated vaccine is therefore being developed. A chimeric vaccine in which Japanese encephalitis structural proteins are inserted into the 17D yellow fever vaccine backbone is one of several vaccines to be developed (41). However, with regard to side effects and risk of complications, a live attenuated vaccine might certainly pose more problems. Therefore, a balance between the cost and the expected problems of vaccination should be considered.

Generally, Japanese encephalitis vaccine is an inactivated virus vaccine derived from infected mouse brain to which thimerosal is added as a preservative (42). Studies have shown that this vaccine is 70%-97% effective in preventing the disease (42). According to the study of Hoke et al, the cumulative attack rate for encephalitis due to Japanese encephalitis virus was 51 per 100,000 in the placebo group and 5 per 100,000 in vaccine group (43). The recommended dosage for persons over 3 years of age is three subcutaneous 1 ml doses and the recommended primary immunization series is given at 0, 7, and 30 days (42, 44). For children 1 - 3 years of age a series of three doses of 0.5 ml should be given at 0, 7, and 30 days (42, 44). There is no information on the efficacy and safety of the vaccine in infants under one year and the pregnant women. In these cases, vaccination should be deferred. Vaccination for individuals with symptomatic HIV infection is still controversial. Further studies on this topic are recommended.

The vaccination is also recommended before traveling to the endemic countries. This vaccination remains important in travel medicine (42, 44, 45).

Japanese encephalitis vaccine is recommended for persons who plan to reside for a month or longer in areas where the virus is endemic or epidemic (42, 44, 45).Depending on the epidemic circumstances, vaccine should be considered for persons spending less than 30 days in such areas, but their activities, such as extensive outdoor activities in rural areas, place them in a particularly high risk for exposure group (42, 44, 45). Lo and Gluckman concluded that Japanese encephalitis vaccine should be offered to travelers who plan prolonged trips to rural areas in Southeast Asia or India during the transmission season (45). An abbreviated schedule of 0, 7, and 14 days can be used when the longer schedule is impractical due to time constraints but the last dose should be given at least 10 days before the beginning of international travel to ensure an adequate immune response and an access to medical care in the event of a delayed adverse reaction (42, 44, 45).Among the adverse effects of Japanese encephalitis vaccination, allergy is

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mentioned as a common side effect (46). However, this is mild and is found in less than 5 % of the patients (44). Nakayama and Onoda reported that the incidence of anaphylactic reaction was estimated to be 0.63 per million for Japanese encephalitis virus vaccine (47). Plesner et al found that about one third of the adverse reactions to the Japanese encephalitis vaccine could be attributed to an allergic predisposition in the vaccinated individual (48). They observed that the main risk factors were young age, female gender and previous allergic skin reactions or hay fever (48). Plesner et al concluded that information on the history of allergy in young adults should be considered before a Japanese encephalitis vaccination, the vaccination should be carried out more than a week before departure and antihistamine treatment should be available if an adverse reaction occurs (49). Severe allergy or anaphylaxis can be seen in some cases (49). Sakaguchi and Inouye noted that two patterns of systemic immediate-type reactions to Japanese encephalitis vaccines could be found: one presenting with cutaneous and respiratory symptoms and the other with cardiovascular symptoms without cutaneous and respiratory symptoms (50). They found that the children in the former group had anti-gelatin IgE in their sera, whereas the latter did not (50). In addition to allergy, there are also rare complications of Japanese encephalitis vaccination. Meningoencephalitis (51) and Gianotti-Crosti syndrome (52) are examples of such adverse effects. However, these two complications are extremely rare. Acute metabolic crisis is another extremely rare complication of Japanese encephalitis vaccination (53). This can lead to death and symmetric foci, cystic cavitations with neuronal loss, and vascular proliferation can be observed in postmortem examination (53). However, according to a recent metanalysis of Schiøler et al, serious adverse events were not observed (54). In this report, mild and moderate episodes of injection site soreness, fever, headache, and nausea were reported in less than 6% of children receiving inactivated vaccine compared to 0.6% of unvaccinated controls (54). Similar to yellow fever, although there are reports on the adverse effects of Japanese encephalitis vaccination, the risk to unimmunized individuals either living in or traveling to areas where there is known Japanese encephalitis transmission is far greater than the risk of having a vaccine-related adverse effect.

DENGUE INFECTION

Dengue infection is also a mosquito-borne arboviral infection. Dengue infection poses a variable spectrum of diseases that range from an undifferentiated fever to dengue fever and finally to a potentially fatal dengue shock syndrome (55). At present, dengue infection is reported in more than 100 countries in the world. Malavige noted that 100 million cases of dengue fever and half a million cases of dengue hemorrhagic fever (DHF) occur worldwide annually (56). More than ninety percent of infected subjects are children less than 15 years of age (56). Originally, this disease was classified as a tropical disease of a highly endemic area in Southeast Asia. However, the spreading of the disease to many other regions is reported. This disease has spread throughout the tropical region in the past forty years, well beyond its original home in Southeast Asia (57). Dengue infection has become an important and imported emerging infection in many non endemic areas in recent years. Recently an interesting retrospective study on imported dengue infection has been performed in France (58). They found that dengue infection was increasingly observed in febrile travelers returning from tropical areas, especially those returning from Southeast Asia (58).

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The infection has an incubation period of 5-8 days followed by the onset of a fever, violent headache, chills, and a rash developing after 3-4 days. Generally, most of the dengue infections are classified as dengue fever, usually presented with fever, constitutional symptoms and positive tourniquet test (59 - 61). The fever usually lasts 4-7 days and most people make a complete recovery without complications (59 - 61). However, it can show a number of atypical forms without fever or without clinically significant symptoms (59 - 61). Abnormal laboratory findings included hyponatremia, abnormal liver enzymes and CSF pleocytosis (62). The overall mortality rate was 5% (62). Since dengue infection is still a public health threat and there is no successful method for its control, therefore development of a vaccine is the only hope. There are many interesting recent reports on dengue vaccination. Efforts have been made since the 1940s to develop dengue vaccines (63). However, there have been many problems in its development (63). Immunity acquired from natural infection is specific for each serotype, and as many as three different serotype infections have been reported in one individual (63 – 67). Multivalent dengue vaccines, now in the late stage of development, pose unique vaccine safety challenges in that primary or secondary vaccine failures might place the vaccinated individuals at risk of antibody-dependent enhanced (ADE) wild-type dengue infections (64) It is known that antibodies to dengue viruses at sub neutralizing concentrations enhance dengue virus infection of receptors for the Fc region of IgG (FcγR+) positive cells (65). This phenomenon is called antibody-dependent enhancement (ADE) and occurs when virus-antibody complexes bind to the FcγR via the Fc portion of the Ig (65). It has been hypothesized that ADE may be responsible for the pathogenesis of the severe manifestations of dengue virus infection including dengue hemorrhagic fever/dengue shock syndrome (65). Yang el al proposed that suppression of Th1 response might be involved in the ADE of heterotypic dengue infections (66). ADE should be of great concern, since immunity to one dengue subtype might bring the risk of infection by another subtype. Chen et al found that DEN-1 immune sera at 1:100 and 1:250 could enhance DEN-2 infections in human mononuclear cells (67). For this reason, a tetravalent vaccine may likely be needed (63). Candidate vaccines against the four serotypes have been tested in volunteers and have proven to be immunogenic and safe (63). Although attenuated live virus vaccines are promising, more study is needed regarding their effectiveness and safety (63). Pang noted that several promising vaccine candidates in the form of live attenuated and chimeric ones had been developed and were currently in human clinical trials (68).

In 2004, Blaney et al reported that the rDEN3/4(ME) and rDEN3/4Delta30(ME) antigenic chimeric viruses could be considered for evaluation in humans and for inclusion in a tetravalent dengue vaccine (69). However, significant practical, logistic, and scientific challenges remain before these vaccines can widely and safely be applied to vulnerable populations. Baize et al suggest that a vaccine approach against viral hemorrhagic fevers is feasible, should induce well-balanced immune responses with cellular and humoral components, and should avoid the potential deleterious effects that are associated with such immune responses (70). Dean et al recently administered a live attenuated, chimeric JE vaccine (ChimeriVax)-JE) to nonhuman primates by skin microabrasion and intradermal delivery using microneedles (71). According to this experiment, both cutaneous delivery methods induced mild viremia similar in magnitude to that observed following subcutaneous injection (71). Dean et al concluded that cutaneous delivery might represent a minimally-invasive alternative approach for a vaccine that more closely resembled the natural route of viral infection (71). However, vaccina-

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tion is not the single successful method in the control of dengue infection. Pang proposed that vector control, community education and public health measures must be pursued in parallel with vaccine development (68).

WEST NILE VIRUS INFECTION

Another mosquito-borne infection is West Nile virus infection. This disease is a newly emerging viral infection. West Nile virus infection is caused by a flavivirus namely the one transmitted from birds to humans through the bite of culicine mosquitoes (72). This virus was discovered in the blood of a febrile woman from Uganda's West Nile province in 1937 (72). This virus can cause West Nile fever in humans, and about 1 in 150, the disease can take a severe course associated with symptoms of the central nervous system (encephalitis) and even death, particularly in patients older than 70 years (73). While most humans infected with West Nile virus are asymptomatic, some may develop an influenza-like illness (72). Disease surveillance remains the cornerstone for the early recognition and control of this virus (69). West Nile virus is a common arbovirosis in Sub-Saharan Africa. It has occasionally caused epidemics or epizootics in the horses in Mediterranean region and southern Europe (74). This disease has become an important newly emerging infectious disease in many Western countries in recent years. Unlike other tropical mosquito-borne diseases, the risk of introduction and spread of West Nile virus infection to Western hemisphere may be due to the migration of birds.

In recent years, several large epidemics of West Nile virus have occurred in other regions of the world where this disease was previously absent (75). According to the recent surveillance report, 42 states in USA reported 3,022 cases of human West Nile virus infection in 2007 outbreak to Centers for Disease Control and Prevention (76). It implies the significance of this viral infection in the new world. West Nile virus infection is an arthropod-borne disease causing a wide range of clinical presentations. Infections in humans are usually asymptomatic (74). The most serious manifestation of infection is encephalitis in humans and horses, as well as mortality in birds. Recently, however, a growing number of cases involving central nervous system manifestations and death have been reported in elderly people (74). Fever, general aches, headache, nausea and vomiting were the principal clinical features in about 90 % of the hospitalized cases (77). Neurological complications are severe and problematic in this infection. Ceausu et al noted that fatality rate in the West –Nile virus infected cases was 15.1% in acute encephalitis, 1.8% in acute meningitis and 0% in the acute febrile disease (78).

West Nile virus infection is a zoonotic disease and cannot be easily eradicated. It is preventable in man if its vaccine becomes available. Therefore, there is a need to develop the vaccine. Similar to dengue infection, an effective vaccine for West Nile virus infection is not available. The development of a West Nile vaccine for humans is justified by the uncertainty surrounding the size and frequency of future epidemics (79).Though a few candidate vaccines are under laboratory trial; no vaccine is so far available commercially for the control of West Nile virus infection in humans and animals (80). Monath et al discuss that the infectious clone technology is used to replace the genes encoding the pre-membrane (prM) and the envelope (E) protein of yellow fever 17D vaccine with the corresponding genes of the West Nile virus and the resulting chimeric virus will contain the antigens responsible for protection against West Nile virus while retaining the replication efficiency of yellow fever 17D (79).The chimeric virus repli-

cates in the host like yellow fever 17D but immunizes specifically against West Nile virus (81). Monath et al noted that the ChimeriVax technology was well-suited to the rapid development of a West Nile vaccine, and clinical trials have begun as early as mid-2002 (79, 80). In horse, Ng et al produced a new vaccine using killed West Nile virus. They noted that the vaccine was safe and efficacious with 94% preventable fraction (82). In addition to human vaccination, avian vaccination for West Nile virus infection is also proposed. Johnson proposed that the greatest percentage of seroconversion was observed in the vaccine group that received a dose of 1.0 ml administered thrice, 3 weeks apart (83). In 2007, Okeson et al reported the antibody response of five bird species after vaccination with a killed West Nile virus vaccine (84). According to this work, significant differences in antibody titer over time were detected for black-footed penguins and two flamingo species (84). It is of interest to note that the passive transfer of maternal antibodies to West Nile virus in flamingo chicks is also confirmed (85).

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