

Prospects for dengue vaccines for travelers

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Travel-acquired dengue cases have been increasing as the overall global dengue burden has expanded. In Korea, imported dengue cases have been reported since 2000 when it first became a notifiable disease. During the first four months of 2016, three times more dengue cases were reported in Korea than during the same period the previous year. A safe and efficacious vaccine for travelers would be beneficial to prevent dengue disease in individual travelers and potentially decrease the risk of virus spread to non-endemic areas. Here, we summarize the characteristics of dengue vaccines for travelers and review dengue vaccines currently licensed or in clinical development.

Keywords: Dengue, Dengue vaccines, Travel

Introduction

Dengue virus (DENV) is a single-stranded, enveloped RNA flavivirus, which is endemic in most tropical and subtropical regions of the world [1]. DENV is transmitted to humans mainly by *Aedes aegypti* and *Aedes albopictus* mosquitoes. Infection can be clinically inapparent or can manifest over a wide clinical spectrum including undifferentiated fever, classic dengue fever, dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), and other severe forms of dengue [1,2]. Four different antigenic serotypes (DENV-1 to DENV-4) are known to circulate. Infection by one serotype can lead to long-lasting homotypic immunity but does not provide long-term cross-protective immunity to other serotypes. Secondary infection with a heterotypic serotype is more likely to result in DHF/DSS than the primary infection [1-3].

Dengue is a major global public health threat with the number of cases increasing dramatically over the past few decades. The World Health Organization (WHO) estimates that 50-100 million DENV infections occur worldwide annually and that almost half of the global population is at risk (Fig. 1) [4,5]. Bhatt et al. [6] estimated 390 million infections occurred in 2010, including 96 million clinically apparent cases. Brady et al. [7] estimated 3.9 billion people in 128 countries are at risk of DENV infection. According to an analysis from the Global Burden of Disease Study 2013, dengue was responsible for approximately 576,000 years of life lost to premature mortality (YLL) and 566,000 years lived with disability (YLD) worldwide [8]. Dengue also imposes a substantial economic burden on households and healthcare systems. The overall mean cost of dengue illness was estimated to be \$248 and \$571 for ambulatory and hospital-

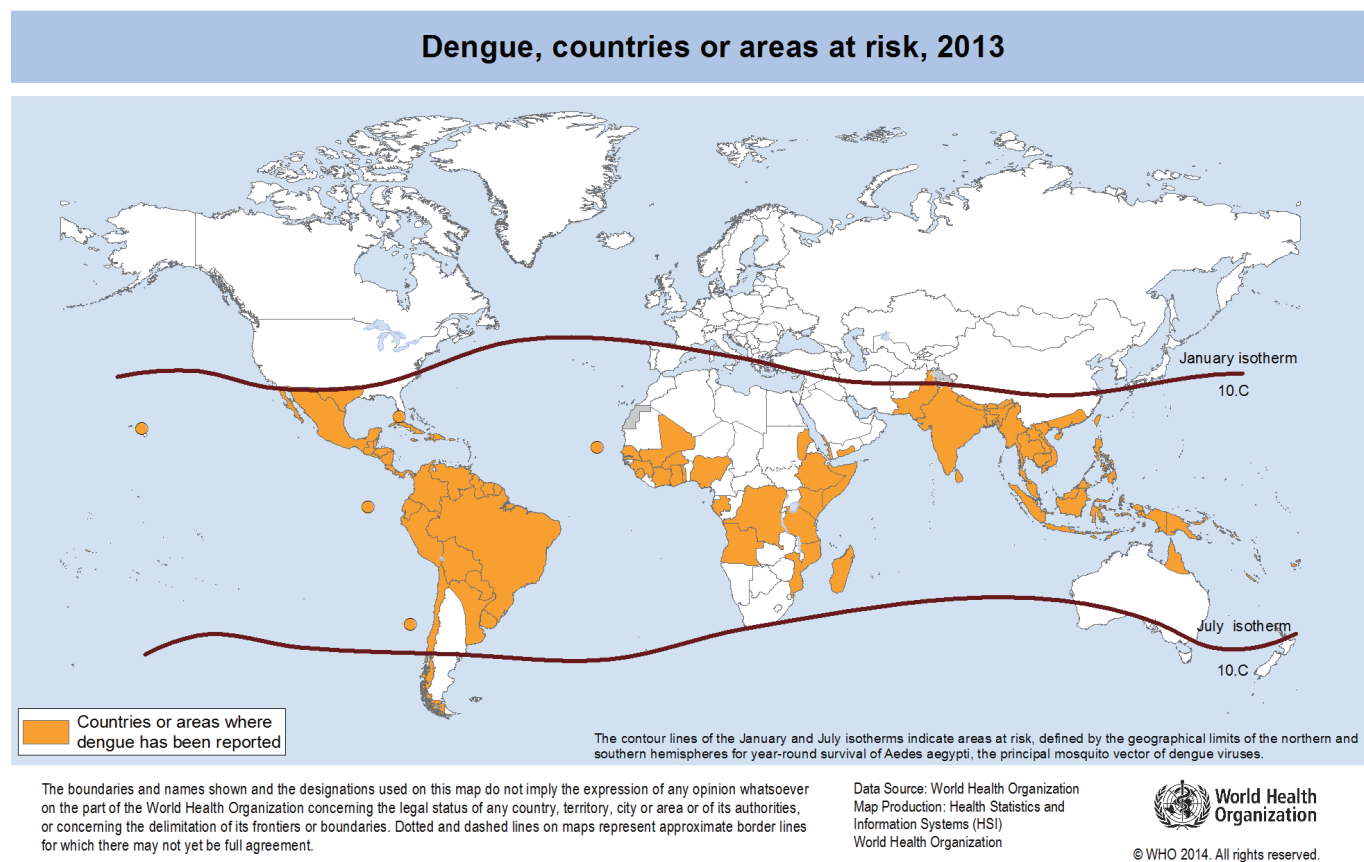


Fig. 1. Countries with reported dengue; areas at risk, 2013. Adopted from Health Statistics and Information System, World Health Organization, 2014 [5].

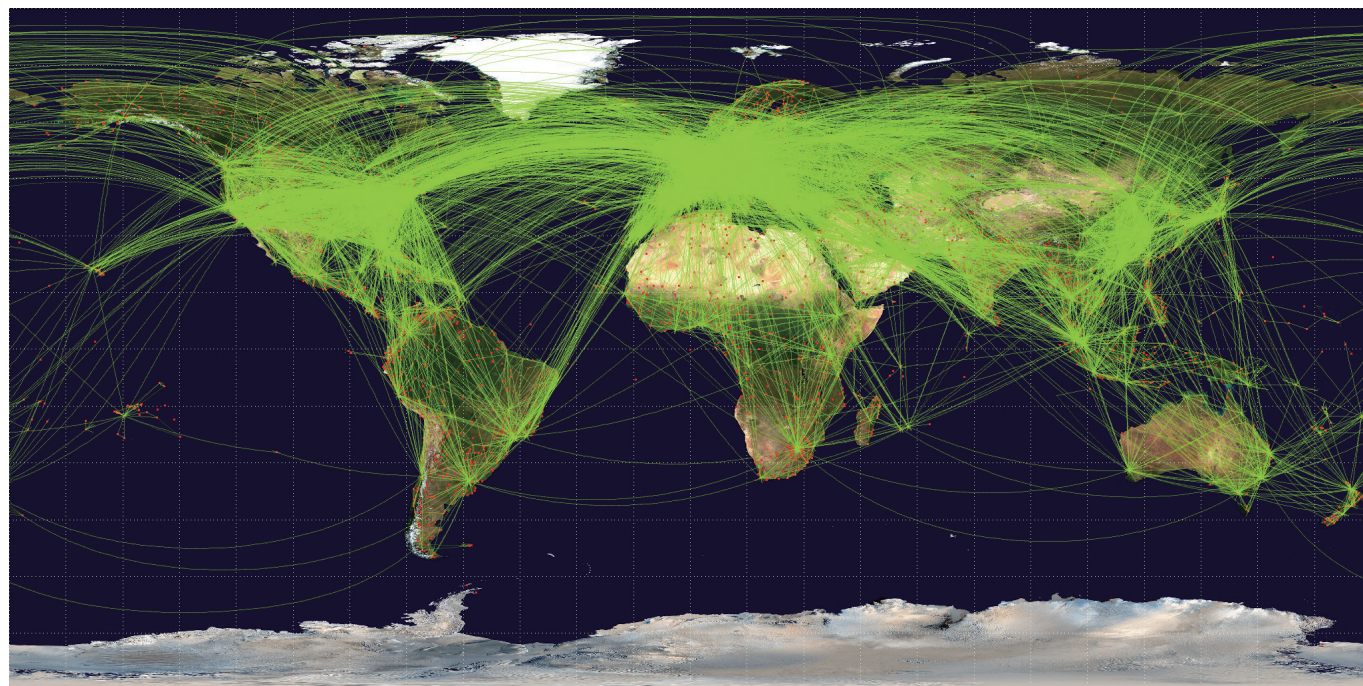


Fig. 2. Global map of air transportation routes. Adopted from Kilpatrick AM, Randolph SE. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. *Lancet* 2012;380:1946-55 [11], with permission of Elsevier.

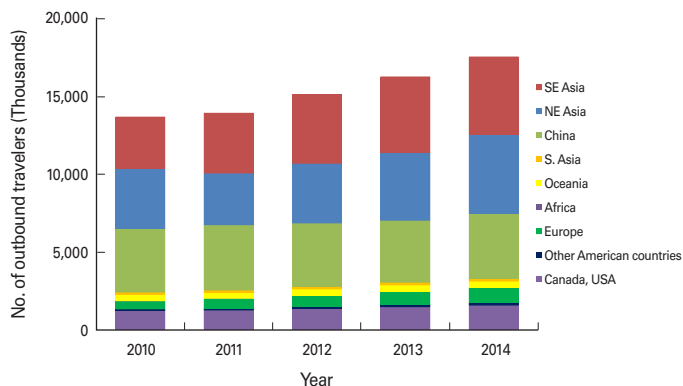


Fig. 3. Korean outbound travelers by destination region, 2010-2014. Source: Korea Tourism Organization. Statistics of international tourism in Korea [21].

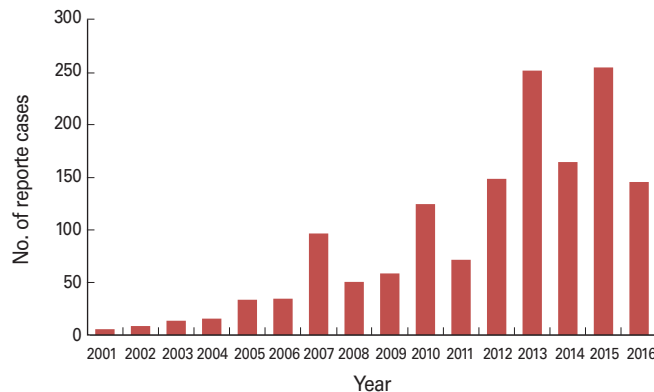


Fig. 4. Reported dengue cases in Korean travelers, 2001-2016 (as of April 2016). Source: Korea Centers for Disease Control and Prevention. Disease Web Statistics System, 2016 [24].

ized cases, respectively [9]. The Global Burden of Disease Study 2013 estimated the total global cost of dengue illness was about \$8.9 billion [10].

Dengue in Travelers

The rapid increase in global trade and travel has facilitated the emergence and re-emergence of infectious diseases such as dengue (Fig. 2) [11]. In 2014, there were approximately 1.1 billion international travelers worldwide which represented an increase of 4.5% from 2013, and about 2.5 times more than in 1990 [12,13]. Europe had the highest number of international arrivals at 582 million, followed by the Asia Pacific region with 263 million, and the Americas with 181 million, the latter representing an increase of 8% from 2013. The number of travelers to Africa and the Middle East increased 2% and 5% from 2013, to reach 56 million and 51 million arrivals, respectively [13].

Among illnesses contracted by international travelers, dengue accounted for about 2.4% of visits to Eurotravnet clinics for travel-related illnesses among European travelers [14]. In a study of 1,207 individuals from the Netherlands who traveled to dengue endemic countries between 2006 and 2007, 14 had positive dengue IgM/IgG enzyme-linked immunosorbent assay with an incidence of 14.6 infections per 1,000 person-months; 6.5% had serologic results suggestive of previous DENV infection [15]. A prospective study of 387 Australian travelers to Asia showed the overall dengue incidence to be 3.4 infections per 10,000 traveler days; seroprevalence was 4.4% in 2007-2010 [16]. Furthermore, over the past decade, autochthonous DENV transmission has occurred in previ-

ously non-endemic countries such as France (2010), Croatia (2010), the United States (Florida, 2009), and Japan (2014) [17-20], presumably initiated by imported cases.

In Korea, travel patterns have reflected the global trends, with the number of outbound travelers increasing by 28.8% from 2010 to 2014, and an even larger increase (50.9%) in travelers to Southeast Asia where dengue is endemic (Fig. 3) [21]. The most common travel destinations for Korean travelers were China, Japan, the United States, Hong Kong, Thailand, Vietnam, and Philippines [22]. Travelers 31-40 years of age (21.1%) constituted the largest age group [22]. The number of travelers was highest in the month of August (9.6%), followed by January (9.1%) and July (9.0%) [22].

The first reported case of dengue in Korea occurred in 1995 in a female traveler returning from Sri Lanka. The second case was reported in 2000 in a sailor who had been working in Africa [23]. Since August 2000, when dengue first became a notifiable disease in Korea, 1,492 cases have been reported in Korean travelers as of April 2016 [24]. No endemic transmission has yet been detected in Korea. However, the number of cases in travelers has increased over the past decade with the highest number (255) reported just last year in 2015 (Fig. 4) [24]. During the first four months of 2016, 146 dengue cases were reported, more than three times the number over the same period in 2015. According to the 2014 Korea Infectious Disease Surveillance Yearbook, dengue was the most commonly reported infectious disease imported from a foreign country, followed by malaria (20%), shigellosis (10%), typhoid fever (6%), hepatitis A (5%), and measles (5%) [25]. Most of these dengue patients had returned from countries in Southeast Asia including the Philippines, Indonesia, Thailand, Ma-

Table 1. Characteristics of dengue vaccines for travelers

Vaccine indication	All ages (adults and children) Immunological naïve travelers Short-term travelers vs. repeat travelers vs. expatriates Differing levels and duration of exposure during travel
Efficacy	High efficacy Protection against both mild and severe disease Protection against infection to limit transmission
Time to protection	Rapid onset of protection
Duration of protection	Protection during the travel period (at a minimum) Longer duration of protection for repeat travelers and expatriates
Doses and schedule	Single dose or few number of doses with compressed schedule Possible boosters prior to travel events Co-administration with other vaccines
Safety, precautions, and contraindications	Very low risk of complications from vaccination Potential use in special populations (immunocompromised and pregnant individuals)

laysia, and Cambodia [23,25,26], and most were between 20 and 39 years of age [25-27]. Dengue cases were reported throughout the year, with higher numbers between July and October [25-27] coincident with higher frequency of outbound travel from Korea along with peak DENV transmission seasons in many Southeast Asian countries.

Need for Dengue Vaccines for Travelers

Given the increasing trends in global international travel, immunologically naïve travelers are being increasingly exposed to endemic pathogens from different regions, posing increasing individual risk for disease. In addition, there is a potential risk of transmission from endemic to non-endemic areas if *Ae. aegypti* or *Ae. albopictus* vectors are present in the non-endemic area. The potential for geographic spread of arboviruses is highlighted by the recent transcontinental migration and explosive expansion of *Aedes*-transmitted chikungunya and Zika viruses from Asia to the Americas [28]. Korea is at risk due to the rapid expansion of international travel by its residents. Using an airport-based risk model, Incheon International Airport in Korea, one of the top international destination airports in a dengue non-endemic country, carries a risk of importing the virus [29]. Although *Ae. aegypti* has not been detected in Korea, *Ae. albopictus* populations have been identified in various provinces of Korea and could serve as a potential local vector [30].

Currently, the main preventive measure against dengue in travelers is avoidance of mosquito bites, such as wearing long-sleeved shirts and long pants, using mosquito repellents, and remaining in indoor screened or air-conditioned areas [31,32].

However, avoidance is difficult because *Ae. aegypti* and *Ae. albopictus* are highly peridomestic, daytime biters [2,33]. Dengue vaccines for travelers will likely be required to prevent disease and mitigate risk of transmission to non-endemic regions.

Considerations for Dengue Vaccines for Travelers

Characteristics of travelers' vaccines would be different from those of the vaccines for wider use in endemic populations. A set of considerations for ideal dengue vaccines for travelers are identified and listed in Table 1.

Vaccine indication

In general, the desired characteristics of vaccines for travelers can differ substantially from those for endemic populations. For example, the target age and immune status are likely to differ in travelers. In endemic populations, children are often the most vulnerable group while adults have often attained a certain degree of natural protective immunity [34]. In contrast, travelers of all ages are likely to be immunologically naïve and susceptible to infection. This difference in travelers is accentuated by the fact that international travelers are also more likely to be adults than children [35]. Thus, vaccines for travelers need to target both adults and children, especially those who are immunologically naïve. In the case of dengue, an additional complicating factor is that secondary DENV infection is more likely to lead to severe disease than primary infection. Although this does not negate the benefit to individual travelers in preventing primary DENV infection, repeat travelers to dengue endemic regions or expatriates who have

already been exposed to DENV may benefit more from dengue vaccination than first time travelers.

Many additional factors specific to each traveler's situation need to be considered when deciding whether to administer a travel vaccine. These factors may relate to the level of exposure risk during travel including the destination country, specific travel locations within the country, type of transportation and accommodations, purpose of travel (e.g., tourism, adventure travel, business, and visiting friends or relatives, etc.), travel conditions, and length of stay. These risk factors may be different for different diseases. For example, the risk of DENV exposure is often higher in urban areas than rural areas, which is the converse of the situation with malaria. Furthermore, since DENV transmission can be spatiotemporally heterogeneous [36], assessing risk based on specific travel locations within a dengue endemic country may be extremely difficult.

Efficacy

Vaccines should ideally be highly efficacious whether for travelers or for endemic populations. However, for travelers, who typically have a much shorter period of exposure and in whom decisions about vaccination are based more on individual factors rather than population-level public health considerations, higher vaccine efficacy is typically required to make the vaccine acceptable to travelers. For malaria, the U.S. military has designated a threshold efficacy of >80% for military personnel and travelers [37]. However, lower efficacies may be acceptable for individual travelers depending on the likelihood of exposure [38]. For example, a traveler who plans to enter an area with an ongoing disease outbreak with high probability of exposure may be more likely to accept a moderately effective vaccine. Therefore, no absolute efficacy threshold is necessarily required for a travel vaccine in all situations. In the case of dengue, vaccine efficacy considerations are complicated by the fact that efficacy may differ for each of the four DENV serotypes [39]. Since dengue epidemiology and circulating serotypes can vary dramatically in different countries and regions, decisions about dengue vaccine use for travel can become complex. Travelers also expect vaccines to be efficacious against both mild and severe disease, since both can have a large impact on travel. Thus, travel vaccines are typically expected to have high efficacy and protect against a wide clinical spectrum of disease.

Vaccination in travelers also has the potential to decrease the risk of spreading the virus from endemic to non-endemic

areas. How much impact the vaccine might have in this way would depend in part on the type of protection produced by the vaccine. If a vaccine is efficacious only against severe disease, then the risk of virus spread to non-endemic areas by infected travelers may only be minimally reduced. For example, DENV has been shown to be transmissible to mosquitoes from asymptomatic and pre-symptomatic individuals, even more than symptomatic patients [40]. Therefore, dengue vaccines that prevent severe disease but not mild or asymptomatic infection may still allow significant transmission to occur.

Time to protection

Vaccines require time to induce a sufficient immune response to elicit protection. According to the International Trade Administration Office of Travel and Tourism Industries from the United States Department of Commerce, preparation for leisure travel typically begins 60-90 days prior to the onset of the trip. However, business travelers start preparation for travel 30 days before departure [41]. Many travelers request vaccinations just days before departure. Therefore, vaccines with rapid onset of immunity are an important requirement for travelers. For vaccine regimens that require more than one dose, the level of immunogenicity and the time to attain that level may differ depending on the dose number. In addition, prior vaccination may affect the time required to achieve an immune response. Booster doses of a previously administered vaccine may elicit a faster immune response than *de novo* vaccination. Therefore, vaccines with booster doses are well suited for use in travelers.

Duration of protection

Although all vaccines should ideally provide long-term protection against disease, a travel vaccine requires protection primarily during the travel period. Therefore, a shorter duration of protection may be sufficient for most travel situations. For example, the Department of Tourism of Thailand, where dengue is hyperendemic, indicates that the average visit lasts for about 10 days [42]. If necessary, booster doses can be administered prior to each travel event. For repeat travelers or expatriates, the duration of protection may need to be longer.

Doses and schedule

The number of doses and schedule is an important factor for travel vaccines [43]. Few numbers of doses and accelerated vaccine schedules can accommodate travelers in need of vaccines on short notice, and encourage compliance with pre-

Table 2. Dengue vaccines currently licensed or in clinical development

Vaccine type	Vaccine	Developer	Approach	Phase	Characteristics related to use in travelers
Live recombinant	Dengvaxia (CYD-TDV)	Sanofi Pasteur	Yellow fever 17D backbone and YF-DENV chimeras	Licensed	Low efficacy in dengue seronegative subjects; three-dose schedule over 12 months impractical for travelers; potential suitability in repeat travelers or expatriates with prior DENV exposure
	TV003/TV005	U.S. NIH/Butantan	Genetic mutations and DENV-2/4 chimera	III	Single dose schedule may be advantage for travelers
	TDV	Takeda	DENV-2 backbone and DENV-DENV chimeras	II	Two-dose schedule over three months may limit acceptance by travelers
Purified inactivated	TDENV-PIV DPIP	GSK/Fiocruz/WRAIR	Formalin inactivated with adjuvant	I	Two-dose schedule over one month may be acceptable for travelers; potential co-administration with other vaccines; possible role in immunocompromised travelers
Protein subunit	V180	Merck	80% E protein recombinant	I	May have similar role as inactivated vaccines for travelers; robustness of immune response uncertain
Plasmid DNA	TVDV	NMRC	Shuffled prM/E expressed in plasmid vector	I	Robustness of immune response uncertain

DENV, dengue virus; U.S. NIH, United States National Institutes of Health; WRAIR, Walter Reed Army Institute of Research; E, envelope; NMRC, U.S. Naval Medical Research Center; prM, premembrane.

travel vaccination [44]. Fewer doses can also reduce costs to the traveler, which in turn can further increase compliance [45]. In addition, as most dengue-endemic areas in the tropics pose a risk for other diseases, suitability for co-administration with other recommended travel vaccines would be relevant for dengue vaccines for travelers. In this regard, non-live vaccines have more flexibility for co-administration than live vaccines.

Safety, precautions and contraindications

The individual risk of infection in travelers is weighed against the risk of complications from vaccination in otherwise healthy individuals. Since the risk of infection in travelers is usually low, the risk of vaccine complications should be similarly very low. This is usually true for most vaccines among general travelers. However, unique to dengue vaccines, there are concerns about the theoretical risk of vaccine-induced immune enhancement leading to more severe disease. It is unclear to what degree this risk exists in various dengue vaccine candidates. However, such a safety signal was indeed detected in very young children during clinical trials of Sanofi Pasteur’s dengue vaccine [46].

In special populations such as immunocompromised individuals [47] or pregnant women [48], the risks of the vaccine are usually not fully evaluated. Conversely, the benefits of vaccination in these groups may potentially be greater than in the general population. The decision-making about vaccine administration in these groups may differ substantially from other groups.

Dengue Vaccines Currently Licensed or in Clinical Development

Development of dengue vaccines has been ongoing for more than 70 years following Dr. Albert Sabin’s initial inoculation with DENV-1 [49]. Dengue vaccine development has been hampered by gaps in the knowledge of dengue pathogenesis, limited understanding of immune correlates of protection, and absence of an adequate animal model for the disease. Despite those multiple hurdles, significant progress in the development of dengue vaccines has been achieved recently. There is now a licensed dengue vaccine available in some endemic countries, and several vaccine candidates are in clinical development (Table 2).

CYD-TDV or Dengvaxia (Sanofi Pasteur)

CYD-TDV (or Dengvaxia) is a tetravalent live recombinant chimeric dengue vaccine based on a yellow fever vaccine strain (YFV17D) backbone with premembrane (prM) and envelope (E) structural protein genes from each of the four DENV serotypes [50]. CYD-TDV underwent two large phase III trials in five countries in Asia (Indonesia, Malaysia, the Philippines, Thailand, and Vietnam) and five countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico) [51,52]. Pooled results during the 25-month active surveillance period from the two trials showed that vaccine efficacy varied depending on serotype, age, baseline dengue serostatus, and severity of disease [46]. Efficacy against symptomatic virologically confirmed dengue among individ-

uals aged 9 years and older was 65.6% (95% confidence interval [CI], 60.7 to 69.9), substantially higher than the efficacy of 44.6% (95% CI, 31.6 to 55.0) in younger children. Dengue seronegative individuals aged 9 years and older had efficacy of 52.5% (95% CI, 5.9 to 76.1), while seropositive individuals in the same age group had efficacy of 81.9% (95% CI, 67.2 to 90.0). Among children younger than 9 years of age, efficacy was 14.4% (95% CI, -111 to 63.5) in seronegative individuals and 70.1% (95% CI, 32.3 to 87.3) in seropositive individuals. Serotype-specific efficacy among children aged 9 years and older ranged from 47.1% (95% CI, 31.3 to 59.2) against DENV-2 to 83.2% (95% CI, 76.2 to 88.2) against DENV-4. Efficacy in children under 9 years ranged from 33.6% (95% CI, 1.3 to 55.0) against DENV-2 to 62.1% (95% CI, 28.4 to 80.3) against DENV-3. Efficacy against severe dengue and hospitalization was substantially higher in individuals aged 9 years and older: 93.2% (95% CI, 77.3 to 98.0) and 80.8% (95% CI, 70.1 to 87.7), respectively; whereas, efficacy among younger children was 44.5% (95% CI, -54.4 to 79.7) and 56.1% (95% CI, 26.2 to 74.1), respectively. Long-term follow-up of hospitalized and severe dengue cases in the Asian phase III trial demonstrated increased risk of hospitalization and severe dengue among the youngest vaccinated children age 2-5 years during the third study year (relative risk, 7.45; 95% CI, 1.15 to 313.80).

Based on these phase III results, CYD-TDV, trademarked as Dengvaxia, was licensed in Mexico, the Philippines, Brazil, El Salvador, and Paraguay, and has been submitted for licensure in other dengue-endemic countries [53]. The vaccine was approved for use in individuals 9-45 years of age (or 9-60 years in Paraguay) living in endemic areas, with three doses administered on a 0/6/12 month schedule. In April 2016, the WHO Strategic Advisory Group of Experts (SAGE) on immunization recommended countries consider introduction of Dengvaxia only in national or subnational geographic settings where dengue is highly endemic [54]. The first school-based dengue immunization program was launched in April 2016 in Marikina, a suburb of Manila, the Philippines [55].

As a travel vaccine, Dengvaxia has substantial drawbacks. Low efficacy in seronegative individuals limits its utility in travelers, who are likely to be dengue naïve [39]. The current three-dose schedule over 12 months is impractical for pre-travel administration and would likely not be acceptable to most travelers [56]. While many travelers to dengue endemic regions are adults [35], a large group of child travelers under 9 years of age would not be eligible for vaccination. Dengvaxia may have a role in repeat travelers or expatriates who may

have had prior exposure to DENV [39], and be more motivated to comply with a three-dose 12-month schedule.

TV003/TV005 (United States National Institutes of Health [U.S. NIH] and Instituto Butantan)

The National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. NIH developed TV003/TV005, a tetravalent live recombinant dengue vaccine candidate [57]. Vaccine serotype constructs for DENV-1, DENV-3, and DENV-4 are based on full length viruses. The DENV-2 component is a chimera, in which the prM and E protein genes of DENV-4 vaccine strain were replaced by those of DENV-2 [53]. Each of the four serotype constructs was optimized in phase I trials assessing various monovalent candidates [58]. Among several different tetravalent formulations evaluated for safety and immunogenicity in phase I, TV003 and TV005 have been further studied [59,60]. TV005 differs from TV003 only in the 10-fold higher dose of the DENV-2 component in TV005. A single dose of TV005 elicited seroconversion rates of >90% for each DENV serotype, with a tetravalent response attained in over 90% of flavivirus-naïve individuals [60].

The U.S. NIH provided a license for the vaccine to in-country vaccine manufacturers in Brazil (Instituto Butantan), Vietnam (Vabiotech), and India (Panacea Biotec and Serum Institute of India), and to Merck [61]. The Brazilian National Health Surveillance Agency (ANVISA) approved a large phase III trial, based on preliminary safety and immunogenicity results from a phase II trial in Brazil [62], as well as the results from clinical studies performed in the United States [59], including a successful challenge study using a DENV-2 challenge strain [63]. Instituto Butantan initiated the phase III trial of TV003 in February 2016, involving 16,944 healthy subjects aged 2-59 years in Brazil [62].

Although the efficacy of TV003/TV005 in different age groups will not be known until results of the phase III trial become available, one potential advantage of this candidate as a travel vaccine is that a single dose appears to induce tetravalent seroconversion in flavivirus-naïve individuals. A single dose schedule in immunologically naïve travelers would be a strong advantage for a travel vaccine.

TDV (Takeda)

Takeda developed a tetravalent live recombinant dengue vaccine candidate (TDV) that consists of an attenuated full length DENV-2 component and three chimeras containing the prM and E protein genes of DENV-1, DENV-3, and DENV-4 expres-

ssed in a DENV-2 backbone [64]. Several phase I trials evaluated different formulations, doses, and routes of administration [65-67]. A phase II study assessed the safety and immunogenicity of TDV in subjects aged 1.5-45 years in Puerto Rico, Colombia, Singapore, and Thailand with a two-dose schedule at 0/90 days [68]. After a single dose, 59%-86% of individuals had tetravalent responses with the greatest increase observed in the youngest age group (1.5-11 years). After the second dose, the seropositivity rate for DENV-1, -2, and -3 in all age groups was over 95%, while DENV-4 seropositivity rate was 72.7%-100%. Neutralizing antibody titers for DENV-1, DENV-3, and DENV-4 increased significantly in seronegative subjects after the second dose. The optimal dosing schedule (0 day, 0/3 months, or 0/12 months) is being further refined in a phase II trial in Asia and Latin America. A multi-country phase III trial is expected to be initiated in the near future [53].

TDV's current two-dose schedule over three months may limit acceptance by travelers. A single dose or compressed two-dose schedule in dengue-naïve adults may need to be evaluated in additional studies to be broadly useful as a travel vaccine.

TDENV-PIV and DPIV (GlaxoSmithKline, Fiocruz, Walter Reed Army Institute of Research)

GlaxoSmithKline (GSK), Fiocruz, and the Walter Reed Army Institute of Research (WRAIR) have been collaborating to develop tetravalent purified inactivated whole virus candidates (TDENV-PIV and DPIV). The DENV strains were grown in Vero (African green monkey kidney epithelial) cells, purified on sucrose gradients and inactivated with formalin [69]. Phase I trials in the continental U.S. and Puerto Rico have been conducted comparing different formulations of TDENV-PIV with various adjuvants (alum, AS01E, and AS03B) [70]. The vaccine is administered in two doses at 0/4 weeks. In dengue-naïve subjects, neutralizing antibody titers were highest at 4 weeks after the second dose, and waned to a plateau by month seven. A phase I/II study has been initiated in the United States to evaluate different formulations and duration of immune responses.

Multiple dosing and the need for boosters are general characteristics of inactivated vaccines [70]. TDENV-PIV and DPIV's two-dose regimen administered over one month may be reasonable as a travel vaccine. Possible limitations in duration of immunity could be overcome with booster doses prior to travel. Co-administration with or around other travel vaccines would likely not be an issue. Inactivated vaccines could also

potentially be used for immunization of immunocompromised travelers [71]. A safe and efficacious tetravalent inactivated dengue vaccine administered in a few doses over a short interval could play a role as a travel vaccine.

V180 (Merck)

Merck's V180 is a tetravalent recombinant subunit protein candidate based on wild-type prM and 80% of E protein (DENV-80E) via expression in the *Drosophila* S2 cell expression system [72]. A phase I trial evaluated monovalent DENV1-80E adjuvanted with alhydrogel at high/low dose in flavivirus-naïve adults in a three-dose regimen at one month intervals. DENV1-80E induced DENV-1 neutralizing antibodies in most individuals, but the titers in the majority of subjects were modest and waned over time [73]. A larger phase I trial of tetravalent V180 with ISCOMATRIX adjuvant was conducted in 98 flavivirus-naïve adults in Australia. Three doses were administered at one month intervals at three different dosages (high/medium/low). One month after the third dose, V180 with ISCOMATRIX resulted in seroconversion rates of 85.7%-100% [74].

Generally, recombinant subunit vaccines require multiple dosing and adjuvant to achieve suitable immunogenicity [70]. They also may have shorter durations of immune response [75], with requirement for booster doses. However, if robust immunogenicity and efficacy can be demonstrated in future studies, a recombinant subunit dengue vaccine may have a role as a travel vaccine, with similar advantages as whole inactivated vaccines.

TVDV (U.S. Naval Medical Research Center)

The U.S. Naval Medical Research Center (NMRC) developed a tetravalent plasmid DNA vaccine candidate using prM and E protein genes expressed in plasmid vector [76]. A phase I clinical trial evaluated safety and immunogenicity of a DENV-1 monovalent candidate in healthy flavivirus-naïve adults using a three-dose schedule at 0/1/5 months, with poor immunogenicity [57]. Although it is possible that TVDV may have a role as a travel vaccine in the future, the available data is currently insufficient to anticipate its potential use as a travel vaccine.

Conclusion

Travel-acquired dengue cases have increased in recent years as the pace of global travel has accelerated. In Korea, the num-

ber of imported dengue cases during the first four months of 2016 was three times higher than in the same period the previous year. Dengue vaccines for travelers would be beneficial to prevent disease in individual travelers and potentially decrease the likelihood of virus spread to non-endemic regions. Currently, one dengue vaccine, Dengvaxia, has been licensed in several endemic countries, while several other vaccine candidates are in clinical development. However, Dengvaxia is not generally suitable as a travel vaccine. Other vaccine candidates may have profiles that better fit a travel indication. Further efficacy trials of these candidates need to be performed to assess their eventual usefulness for both travelers and endemic populations.

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