



Dengue vaccine development: status and future

Introduction

Dengue is globally the most frequent arboviral disease, present in more than 128 countries in the tropics and subtropics and poised to increase even further in terms of incidence and continued geographic expansion [1, 2], thereby also affecting international travelers [3, 4]. The four dengue virus serotypes belong to the family of *Flaviviridae* and are genetically distinct but still closely related. Infection with any of the four dengue virus serotypes may be asymptomatic or may result in clinical manifestations ranging from a mild undifferentiated febrile syndrome to severe dengue. Severe dengue is characterized by plasma leakage, hemorrhagic tendencies, organ failure, shock, and, occasionally, death [5]. Patients with a second dengue infection with a dengue serotype different from the first are at increased risk for severe dengue. The hallmark of severe dengue is capillary leakage leading to shock and, if not managed well, death. The pathomechanism of severe dengue is still poorly understood, although the most plausible hypothesis is antibody-dependent enhancement in secondary infections [6]. Because effective vector-control measures are not scalable or sustainable, community-based approaches have led to mixed results [7, 8], and promising novel strategies such as *Wolbachia* are still under development [9], a dengue vaccine would appear to be the best intervention. The purpose of this review is to elaborate on the first licensed dengue vaccine and review second-generation dengue vaccines, both in the context of endemic populations as well as international travelers.

Rationale for a dengue vaccine

According to modeling estimates, about 50–100 million dengue cases occur every year [10]. The incidence of dengue has increased greatly, with the number of cases more than doubling every decade, from 8.3 million (3.3–17.2 million) apparent cases in 1990 to 58.4 million (23.6–121.9 million) apparent cases in 2013, responsible for 1.14 million disability-adjusted life-years [10]. In dengue-endemic countries, approximately 10% of febrile episodes in children and adolescents are due to dengue, with a higher incidence in Asia (4.6 episodes per 100 person-years) compared to Latin America (2.9 episodes per 100 person-years); the percentage of dengue infections requiring hospitalization was 19% in Asia versus 11% in Latin America [11]. Many dengue infections lead to hospitalizations, which can overwhelm weak health care structures, in particular during times of outbreaks. Given the unpredictability of outbreaks, the increasing magnitude and frequency of such outbreaks, and the current lack of highly effective and sustainable vector-control interventions, there is a clear indication for a dengue vaccine for endemic populations.

Challenges and hurdles in the development of dengue vaccines

Several difficulties have hampered the development of a dengue vaccine. One challenge is the lack of an appropriate animal model and poor knowledge of correlates, both for protection and disease enhancement [12]. But the biggest hurdle is the interaction among the four

serotypes. As a tetravalent immune response is desired, when a mixture of all four serotypes in a tetravalent live attenuated vaccine is given, each component would need to independently result in four different monotypic immune responses that are solid to each serotype. This has, unfortunately, proven to be difficult to achieve.

Dengue vaccine development

Despite more than 30 years of efforts using various vaccine platforms including inactivated, DNA, and live vaccines, only live attenuated vaccines have entered phase 3 trials. Three live attenuated dengue vaccines are now in late-stage development, with one candidate having completed phase 3 trials including long-term follow-up of 5 years: CYD-TDV by Sanofi Pasteur, Lyon, France, with the trade name of Dengvaxia.

CYD-TDV dengue vaccine

CYD-TDV, a tetravalent live attenuated vaccine with a yellow fever 17D backbone, is the first dengue vaccine to be licensed. Phase 3 trials revealed a vaccine efficacy that depended on age, serostatus, and serotype but also showed a population-level benefit [13]. Interference manifested by asymmetric immunological responses to the mixtures of four dengue vaccine viruses was recognized as a possible reason for this varied vaccine performance [14]. Post hoc retrospective analyses of the long-term safety data using a novel nonstructural protein (NS1) antibody assay revealed an excess risk of severe dengue in those who were seronegative at baseline, which means

those who were dengue-naïve at the time of administration of the first dose [15]. This increased risk was observed starting from 30 months after administration of the first dose. The reasons for the excess cases are not fully understood, but a plausible hypothesis is that Dengvaxia may trigger an immune response to dengue in seronegative persons that predisposes them to a higher risk of severe disease, analogous to what is seen in natural secondary dengue infections. In other words, it is plausible that Dengvaxia results in a “primary-like” silent infection (which live attenuated vaccines often elicit) [16]. A subsequent infection with the first true wild-type dengue virus would then be a “secondary-like”, clinically more severe dengue illness. It is not the vaccine itself that causes excess cases, but rather the vaccine’s induction of an immune status that increases the risk that subsequent infections will be more severe.

Despite licensure in 20 dengue-endemic countries to date, CYD-TDV has been introduced in only two subnational public health programs: those in the Philippines and in Brazil. After a media release in November 2017 about the safety concern for seronegative persons, the Philippines decided to suspend its program, while Brazil completed its program but has not expanded it. The media release resulted in a major public outcry in the Philippines, with heightened anxiety and lack of confidence around vaccines in general [17], which led to the subsequent resurgence of measles in the Philippines, reflecting the global resurgence of measles [18–20]. Communication around the introduction of any new vaccine, but especially those vaccines with partial efficacy or complex vaccine performance, needs to be improved to avoid public distrust and lack in vaccine confidence.

The World Health Organization recommends that for countries considering CYD-TDV vaccination as part of their dengue-control program, a prevaccination screening strategy is recommended so that only dengue-seropositive persons are vaccinated [21]. The challenge is now to urgently develop and license rapid diagnostic tests to support such a prevac-

ination screening strategy [22]. In May 2019, the U.S. Food and Drug Administration (FDA) approved CYD-TDV for use in seropositive individuals 9–16 years of age living in endemic areas of the United States. The European Medicines Agency also endorsed the use of this vaccine in seropositive individuals only.

The World Health Organization has published guidance on evaluating the quality, safety, and efficacy of live attenuated dengue tetravalent vaccines, including the need for baseline blood samples from all participants for a priori analysis plans stratified by serostatus, as well as long-term follow-up for 3–5 years after the first dose [23]. This document will guide vaccine developers in trial design and facilitate regulatory review to enable broader public health recommendations for second-generation dengue vaccines. Indeed, the phase 3 efficacy trials of the two second-generation dengue vaccines have incorporated all these requirements. Furthermore, there is a need for the development of standardized end points for vaccine and other interventional trials, including the need for subsequent validation with prospective data sets [24]. The complexity of developing moderate disease research end points for dengue is particularly challenging.

Second-generation dengue vaccines

Two live attenuated dengue vaccines are now in phase 3 trials. One such live attenuated dengue vaccine is being developed by Takeda: DENVax vaccine consists of an attenuated DENV-2 (DEN2-PDK-53), whereby three chimeric viruses containing the prM and envelope proteins of DENV-1, DENV-3, and DENV-4 are inserted into the DEN2-PDK-53 backbone. The difference from Dengvaxia, therefore, is the presence of nonstructural (NS) proteins due to the DENV2 backbone. The conserved NS proteins within the dengue backbone may well be required to generate T-cell-mediated responses to dengue infection, and antibodies against NS1 are associated with cross-protective humoral immune responses [25]. This vaccine has performed well in phase 1

and phase 2 clinical trials, with high titers of neutralizing antibody to all four serotypes in nonhuman primates and humans, including cross-reactive T-cell-mediated responses that may be necessary for broad protection against dengue fever [25, 26]. The vaccine efficacy is currently being tested in approximately 20,000 recipients in phase 3 trials in Asia and Latin America using a two-dose regimen given 3 months apart. Efficacy data for the first 18 months are imminent.

The other tetravalent live attenuated dengue vaccine was developed by the U.S. National Institutes of Health (NIH) and is currently in a phase 3 trial in Brazil, but it was also licensed to Merck and various other vaccine manufacturers for further development outside Brazil. This vaccine consists of three full-length dengue virus (DENV) serotypes attenuated by one or more deletions in the 3′ untranslated region with DEN1Δ30, DEN2Δ30, and DEN4Δ30, while the fourth component is a chimeric virus in which the prM and E proteins of DENV-2 replace those of DENV-4 in the DEN4Δ30 background [27]. This vaccine performed well and was safe in phase 1 and phase 2 trials [28]. A single dose induced robust tetravalent antibody and cellular T-cell responses and resulted in 100% efficacy in a human challenge study [29]. The capacity to elicit CD4+ cell responses closely mirrored those observed in a population associated with natural immunity [30].

The advantages of these second-generation dengue vaccines are the inclusion of NS proteins of the dengue backbone and more convenient dosing, with reduced numbers of doses needed: While Dengvaxia is licensed for three doses 6 months apart, the Takeda vaccine is currently being considered for two doses 3 months apart and the NIH vaccine for a single dose. Whether these second-generation vaccines will provide balanced high protection against all four serotypes and thus overcome the serostatus-dependent problem of CYD-TDV remains unknown and can be addressed only by the long-term results of the pending phase 3 trials.

Dengue vaccines for travelers

Many dengue-endemic countries are commonly visited travel destinations, and therefore dengue has become a frequent cause of febrile illness among international travelers [31]. An increase in hospitalizations and health care visits for dengue has been seen in American [32] and European travelers [33, 34]. GeoSentinel is an international network of travel medicine providers [35] that has also reported an increase in dengue over the past decade [36]. Dengue can affect tourists, business travelers, expatriates [37, 38], pilgrims [40], and migrants, including those visiting friends and relatives [39], and can affect both adults and children [4, 41, 42]. Interruption of travel, premature return, hospitalization during or after travel, and out-of-pocket expenses are the result [43]. With an incidence of about 1–5% for travelers to dengue-endemic countries [31], dengue is much more frequent than many of the other travel-associated vaccine-preventable diseases, such as hepatitis A, yellow fever, and Japanese encephalitis [44, 45]. Vaccination would be of clear benefit to travelers, but the benefit versus risk needs to be clearly weighed [46]. Although vaccination is now licensed in Europe by the European Medicines Agency and in the United States by the FDA, and is also licensed in Australia, it has not yet been endorsed for the travel medicine indication. Furthermore, the only currently licensed dengue vaccine, CYD-TDV, should be used only in seropositive travelers [47]. Most travelers, however, are seronegative [48]. Furthermore, the dosing schedule of three doses 6 months apart for CYD-TDV renders the use of such a vaccine difficult in the travel medicine context. A safe and efficacious vaccine that can be used regardless of serostatus would enhance the use of a dengue vaccine in travelers [49]. Travelers should be advised to take daytime personal protective measures against mosquito bites [50].

Conclusions

Given the unpredictability of dengue outbreaks, the increasing magnitude and fre-

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Abstract

Dengue, the most common arbovirus, represents an increasingly significant cause of morbidity worldwide, including in travelers. After decades of research, the first dengue vaccine was licensed in 2015: CYD-TDV, a tetravalent live attenuated vaccine with a yellow fever vaccine backbone. Recent analyses have shown that vaccine performance is dependent on serostatus. In those who have had a previous dengue infection, i.e., who are seropositive, the efficacy is high and the vaccine is safe. However, in seronegative vaccinees, approximately 3 years after vaccination the vaccine increases the risk of developing severe dengue when the individual experiences a natural dengue infection.

The World Health Organization recommends that this vaccine be administered only to seropositive individuals. Current efforts are underway to develop rapid diagnostic tests

to facilitate prevaccination screening. Two second-generation dengue vaccine candidates, both also live attenuated recombinant vaccines in late-stage development, may not present the same limitations because of differences in the backbone used, but results of phase 3 trials need to be available before firm conclusions can be drawn.

Dengue is increasingly frequent in travelers, but the only licensed dengue vaccine to date can be used only in seropositive individuals. However, the vast majority of travelers are seronegative. Furthermore, the primary series of three doses given 6 months apart renders this vaccine difficult in the travel medicine context.

Keywords

Severe dengue · CYD-TDV · Antibody-dependent enhancement · Travelers · Live attenuated chimeric dengue vaccine

Entwicklung von Impfstoffen gegen Dengue: aktueller Stand und Zukunft

Zusammenfassung

Das Dengue-Virus, das am meisten verbreitete Arbovirus, stellt weltweit eine zunehmende Ursache für Morbidität dar, auch bei Reisenden. Nach jahrzehntelanger Forschung wurde 2015 der erste Impfstoff gegen Dengue-Fieber zugelassen: CYD-TDV, ein tetravalenter, attenuierter Lebendimpfstoff auf Basis des Gelbfieber-Impfvirus („backbone“). Neueste Analysen haben gezeigt, dass die Performance des Impfstoffs vom Serostatus abhängig ist. Bei Menschen, die bereits eine Dengue-Infektion hatten und seropositiv sind, ist die Wirksamkeit hoch und der Impfstoff sicher. Bei seronegativen Impfungen erhöht der Impfstoff jedoch im Fall einer nachfolgenden Dengue-Wildvirusinfektion das Risiko für eine schwere Dengue-Erkrankung etwa 3 Jahre nach der Impfung. Die Weltgesundheitsorganisation empfiehlt daher, den Impfstoff nur an seropositive Menschen zu verabreichen. Derzeit wird intensiv an der Entwicklung von Schnelltests gearbeitet, um das Screening vor der Impfung zu erleichtern. Zwei Dengue-Impfstoffkandidaten der zweiten Generation,

beide ebenfalls attenuierte rekombinante Lebendimpfstoffe, befinden sich in der Spätphase der Entwicklungspipeline und könnten aufgrund der Unterschiede der verwendeten „backbones“ nicht dieselben Limitierungen aufweisen; es müssen aber die Ergebnisse der Phase-3-Studien abgewartet werden, um dies sicher beurteilen zu können. Dengue-Fieber tritt immer häufiger bei Reisenden auf. Die überwiegende Mehrheit der Reisenden ist jedoch seronegativ, weshalb bei ihnen der bisher einzige zugelassene Impfstoff gegen Dengue-Fieber nicht eingesetzt werden kann. Darüber hinaus sind für die Grundimmunisierung drei Impfdosen nach dem Schema 0-6-12 Monate erforderlich, wodurch der Einsatz dieses Impfstoffes im reisemedizinischen Kontext schwierig ist.

Schlüsselwörter

Schweres Dengue-Fieber · CYD-TDV · Antibody-dependent enhancement · Reisende · Attenuierter chimärer Dengue-Lebendimpfstoff

quency of such outbreaks, and the high morbidity of this disease that can overwhelm already weak health care systems, a dengue vaccine is urgently needed. Furthermore, dengue vaccines would be indicated for international travelers, in particular those who have already had one primary infection in order to reduce the risk of severe dengue as a result of a second infection during repeat travel. The second-generation dengue vaccines may overcome some of the shortcomings of the first licensed dengue vaccine; however, these vaccines will not be available for at least another couple of years. Phase 3 efficacy trials of second-generation dengue vaccines need to be analyzed and stratified by serostatus, and long-term data of at least 3 years following the first dose should be available before such vaccines are licensed. A safe and efficacious vaccine that can be used regardless of serostatus would enhance the use of a dengue vaccine in travelers.

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Compliance with ethical guidelines

Conflict of interest A. Wilder-Smith serves as a consultant to the World Health Organization with regard to dengue vaccines. The views expressed in this article are those of the author and do not necessarily represent the decisions or policies of the World Health Organization.

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