Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Status of vaccine research and development of vaccines for dengue

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ARTICLE INFO

Article history:
Received 17 August 2015
Accepted 30 December 2015
Available online xxx

Keywords:
Dengue vaccine
Vaccine development
Clinical pipeline

ABSTRACT

This review on the dengue vaccine pipeline was a solicited article and drafted based on the pre-defined template for PD-VAC.

1. About the disease and pathogen

Dengue virus is a single-stranded RNA virus in the genus *Flavivirus*, family *Flaviridae*. There are four distinct serotypes (DENV1–DENV4). They are antigenically diverse and only share about 60–75% identity at the amino acid level [1]. Due to genetic variations leading to changes in viral fitness, virulence, and transmission, serotypes and lineages may manifest different patterns of clinical disease and severity. The mature spherical dengue viral particle contains multiple copies of the three structural proteins (capsid, C, prM, the precursor of membrane, M, protein and envelope, E), as well as a host-derived membrane bilayer and a single copy of a positive-sense, single-stranded RNA genome. Human antibodies raised against the DEN virion are mostly targeted at the E and prM proteins.

The virus is transmitted to humans by infectious bites of *Aedes* mosquitoes, in particular *Ae. aegypti* but also *Ae. albopictus*. These vectors are urban day-biting mosquitoes, such that insecticide treated bednets, which have been very important for malaria control, are ineffective [2]. Infected humans are the main carriers and multipliers of the virus, which then transmit DENV to uninfected mosquitoes for subsequent transmission. The geographic distribution of dengue is determined in large part by the vector [3]. During the past five decades, the incidence of dengue worldwide has increased 30-fold [4]. In 2013 the WHO ranked dengue as the fastest spreading vector-borne viral disease, with an epidemic potential. This expansion is believed to be due to global trade (increased transportation and expansion of the vectors), increased global travel (importations of dengue virus to new areas), and urbanization (multiple transmission opportunities from an infected mosquito), possibly enhanced by global warming [5]. Today, all five WHO regions are affected by dengue, with nearly 4 billion people believed to be at risk of dengue infection. The numbers of dengue cases submitted to WHO are underreported and many cases are misclassified because illness is mild or cannot be differentiated from other viral diseases that manifest high fever [6]. One recent modelling estimate suggests 390 million dengue infections occur globally each year, of which 96 million are clinical, and up to one million considered severe [7]. Dengue control is a major public health priority in disease endemic countries. However, the burden of disease in many regions, particularly Africa, is poorly understood.

In endemic areas, dengue has been traditionally a pediatric disease of children less than 15 years of age. However, in some settings there has been a shift toward older age groups; it has been suggested this is related to changing demographics, including smaller susceptible birth cohorts and a larger immune aging population [8].

Dengue can be diagnosed either by virus isolation, serology (MAC-ELISA, IgG ELISA, NS1 ELISA, and PRNT), or molecular methods (RT-PCR). PCR is considered the gold-standard for dengue diagnosis (80–90% sensitivity and 95% specificity if applied in the adequate time window), as serological tests suffer from cross-reactivity, variable sensitivity by timing of specimen collection, and the need for multiple samples (IgG acute and convalescent samples) [9,10]. Due to limited capacity for PCR around the world, definitive dengue diagnosis is difficult in many settings.

Clinical dengue, in particular during epidemics, puts a significant strain on health care facilities. WHO classifies dengue into two categories, dengue (with or without warning signs) and severe

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http://dx.doi.org/10.1016/j.vaccine.2015.12.073

Please cite this article in press as: Vannice KS, et al. Status of vaccine research and development of vaccines for dengue. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2015.12.073

dengue [9]. Dengue without warning signs can still lead to significant patient discomfort and debilitation from high fever, vomiting, myalgia, and joint pain lasting 3–7 days, leading to school absenteeism and loss of work. Because it is difficult to know which dengue cases will become severe, non-severe patients are often admitted to the hospital for monitoring. Severe dengue can be life threatening due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, and/or organ impairment. Through improved supportive clinical case management, case fatality rates from severe dengue have decreased from more than 20% to less than 1% [11,12]. Proper maintenance of the patient's body fluid volume is critical to patient success.

The strain on the health system and wider economic consequences of non-severe and severe dengue are significant. The cost of illness includes lost wages and decreased productivity as well as care-seeking and direct medical expenses. Sixty percent of the economic strain is attributable to indirect costs [13]. The global economic burden is not well described, but in the Americas alone it is estimated at $2.1 billion USD each year (Table 1).

Natural immunity to wild-type infection is not completely understood. Humans infected with one serotype of dengue appear to remain protected for the rest of their life to subsequent symptomatic infection with the infecting serotype (homotypic immunity) [14]. Following a first clinically manifested infection, there is a period of cross-protection (heterotypic immunity) against symptomatic infection with the other three serotypes for approximately two years [15]. As cross-protection wanes, individuals who have only had a primary infection are at an increased risk of severe dengue with a secondary infection of a heterologous serotype [16]. It is commonly believed that this increased risk is due to antibody-dependent enhancement of infection, but other mechanisms may contribute [1]. Following a secondary infection, symptomatic dengue due to a third or fourth infection is rare. Thus it is presumed that a secondary infection reinforces non-type specific immunity that provides additional protection against the remaining serotypes (multitypic immunity) [14]. This phenomenon with wild type infection has been an important consideration for the strategy to develop a vaccine and the necessary follow up in clinical trials [17].

2. Overview of current efforts

2.1. EITHER Vaccines currently available and their limitations OR Biological feasibility for vaccine development

In December, 2015, the first dengue vaccine, Dengvaxia® (CYD-TDV) developed by Sanofi Pasteur, was licensed in Mexico [18]. The vaccine was licensed in individuals 9–45 years living in endemic areas (defined as ≥60% seroprevalence for dengue). As of writing the regulatory file for CYD-TDV is under review by several additional endemic countries National Regulatory Authorities (NRA).

CYD-TDV is a 3-dose live recombinant tetravalent dengue vaccine administered on a 0/6/12 month schedule. It is based on the YF17D backbone, which is also the basis for the licensed JE vaccine IMOJEV [19]. CYD-TDV includes all three structural proteins, but because of the YF backbone, there are no dengue non-structural proteins included. This vaccine has been evaluated in two large pivotal Phase 3 trials in 5 countries in Asia and 5 countries in Latin America, in participants aged 2–16 across the two trials [20,21]. Pooled vaccine efficacy against symptomatic virologically-confirmed dengue (VCD) of any serotype in the year starting 1 month after the third dose was 59.2% (95%CI 52.3, 65.0) [22]. Vaccine efficacy varied by participant age, serostatus at baseline, severity of dengue disease, and infecting serotype. Vaccine efficacy was higher against serotypes 3 and 4 (71.6% and 76.9%, respectively) than against serotypes 1 and 2 (54.7% and 43.0%, respectively), with the lower confidence bound above zero for all serotypes. Surprisingly, vaccine efficacy was substantially higher among participants who had already been exposed to dengue (pooled VE from immunological subset: 78.2%, 95% CI 65.4, 86.3) compared with participants who were naive at baseline (pooled VE: 38.1%, 95% CI −3.4, 62.9). Interim results from long-term safety follow up demonstrated an elevated risk of hospitalization and severe dengue among 2–5 year old participants (at vaccination) in the third year after receipt of the first dose (RR = 7.45, 95% CI 1.15, 313.80). This younger age group was thus not included in the initial indication. No safety signals were identified in older age groups.

The mechanism behind the imbalance seen in the youngest age group is not currently understood, although there are a number of hypotheses, including age-specific susceptibility to severe disease, serostatus at baseline, waning immunity, and clustering of cases in the CYD group [23,24]. While differences in risk are associated with age, there may be factors in addition to or highly correlated with age that are important. There is a need to better characterize and assess the potential increased risk of dengue among some vaccinees looking at both characteristics of the vaccine and vaccinees, which will also inform any implications for other vaccine candidates [25]. An optimal pediatric vaccine would need to elicit long-term protection against dengue from all four serotypes in seronaive individuals, and hence should have strong immunological priming capacity against all four DENV serotypes.

In addition, six other candidates are in clinical development using a variety of technological approaches. A strong case for the feasibility of developing a dengue vaccine can be made based on the assumed life-long homotypic immunity conferred by natural infection [14]. Due to the theoretical risk of immune enhancement, the dogma has been that a tetravalent vaccine inducing a balanced immune response was needed [26]. The interim results of long-term follow up of CYD-TDV show these concerns to be relevant (though not confirmed), and ongoing/future development efforts will need to have practices in place to closely monitor for changes in risk, including in subgroups, and make all efforts to ensure the safety of trial participants [27].

2.2. General approaches to vaccine development for this disease for low and middle income country markets

Many dengue-endemic countries are middle-high income economies and provide a large market to drive development. Candidates under development are being designed primarily for use in endemic settings, which are predominantly low and middle income countries. For this reason and for easier implementation into immunization programs, there are efforts to minimize the number of doses needed, ideally for single-dose vaccines. One candidate vaccines have also been studied for having a low cost of goods [28]. Given the age distribution of symptomatic dengue, which is quite broad and dependent upon on the transmission setting, there is attention both to vaccine use in young children as well as in adults. There is consensus that a vaccine that can be provided in early childhood is needed for those countries in which substantial disease in childhood would require early vaccination. Live attenuated candidates under development have ongoing age de-escalation studies with a target lower bound of 1 or 2 years due to interference with maternally derived antibodies and ADE and are both currently being evaluated as single dose vaccines [29–32].

3. Technical and regulatory assessment

While many dengue vaccine trials are conducted under US Investigational New Drug (IND) supervision, dengue vaccines have

Please cite this article in press as: Vannice KS, et al. Status of vaccine research and development of vaccines for dengue. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2015.12.073