Review Article *Goud et al., 7(12): Dec., 2016:5349-5354]*
CODEN (USA): IJPLCP **ISSN: 0976-7126**

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

The recent development of dengue vaccination

Pawan Goud*, Javed Khan Pathan, Sapna Malviya and Anil Kharia
Modern Institute of Pharmaceutical Sciences, Indore (MP) - India

Abstract

Dengue has a vital health problem across the globe, approximately half of the world's population. The expanding burden of dengue has highlighted the need for new drugs and vaccines, to prevent dengue. Today it is the world's most crucial arboviral disease as number of people affected over the past 50years. There were approximately 390 million infections in 2010. Due to globalization, trade, travel, demographic trends and warming temperatures it causes spreading of the primary vectors Aedes aegypti and Aedes albopictus, responsible to cause dengue. A tetravalent dengue vaccine demonstrated its protective efficacy in phase III studies. Results of studies were used to derive vaccination in the five Asian countries, wis-to-wis Indonesia, Malaysia, Philippines, Thailand, Vietnam. Moreover five Latin American countries were also involved wis-to-wis Brazil, Colombia, Honduras, Mexico and Puerto Rico. Dengue transmission were estimated, using data collection during the phase III studies, its parameters related to vaccine efficacy and levels of the disease. All vaccination programs explored significant reductions in dengue cases at the population level over the first 10 years followed by vaccination. The most efficient age for vaccination varied according to transmission intensity and 9 years was close to the most efficient age. The combinations of routine vaccination and large campaigns were organised so that a rapid reduction of dengue has been found after vaccine administration. Recently, the first dengue vaccine candidate was undergone in Phase 3 clinical trials and other vaccine candidates are under the clinical investigation. Lot of candidates are evaluated in preclinical development, based on diverse technologies, with satisfactory results in animal models. There is tremendous opportunity in clinical trials and eventually could results in be next-generation dengue vaccines.

Key words: Dengue, Vaccination, Development

Introduction

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 [1]. 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 [2].Worldwide, dengue is the most important vector-borne viral disease that is transmitted to humans by mosquitoes. The burden of disease has increased an estimated 30-fold over the past 50 years [3].

*** Corresponding Author**
Email: javedcology@gmail.com

Globalization ,trade, urbanization, travel ,demographic change, inadequate domestic water supplies and warming temperatures are associated with the spread of the main vectors Aedes aegypti and Aedes albopictus [4]. Aedes aegypti, originally from Africa ,and Aedes albopictus, from Asia ,rapidly expanded their range over the past 50 years, Dengue virus (DENV) also spreads rapidly via infected travelers [5], whose numbers have increased over recent decades [6]. Climate change may lead to changes in these determinants of dengue transmission by multiple, inter-related mechanisms.

One recent prediction of the global burden suggests approximately390 million dengue infections each year (95% credible interval284–528), of which 96 million (C.I. = 67–136) are clinically apparent [7]. To date, specific dengue therapeutics are not available and dis-ease prevention is limited to vector control and personal protectivemeasures with little data to support their impact on clinical disease [8]. Thus, the development of a safe and effective dengue

vaccinewould represent a major advancement in the control of the disease

The development of a safe and effective dengue vaccinewould represent a major advancement in the control of the disease.One candidate has been evaluated in Phase 3 trials in Asia and LatinAmerica. The vaccine, a three-dose live recombinant tetravalentdengue vaccine based on the YF17D backbone (CYD-TDV), demonstrated efficacy in the first year of the observation period (from 28days after the third dose) of 56.7% in Asia [9] and 60.8% in LatinAmerica [10]. In longer-term hospital-based follow up, a signal ofincreased risk of severe and hospitalized dengue was identifiedin the 2–5 year age group in Asia, with a relative risk of hospitalized dengue in year 3 post-dose 1 of 7.45 (95% CI 1.15–313.80) [11].The mechanism behind this increased risk is not understood [12], and the sponsor has recommended an indication for individuals 9+years of age [13]. Second generation vaccines may improve on therange of the age indication, dose-scheduling, or efficacy, as well as contribute to vaccine supply security.This is an update of a 2011 review focusing on dengue vaccinecandidates in preclinical development [14]. It is based on publisheddata and written updates solicited from vaccine developers andresearchers. Primary focus was given to candidates who are inactive development and have been evaluated in non-human primate (NHP) models (Table 1)

Disease and pathogen

Dengue virus is a single-stranded RNA virus in the genusFlavivirus, family Flaviridae. There are four distinct serotypes(DENV1–DENV4). They are antigenically diverse and only shareabout 60–75% identity at the amino acid level [15]. Due to geneticvariations leading to changes in viral fitness, virulence, and trans-mission, serotypes and lineages may manifest different patternsof clinical disease and severity. The mature spherical dengue viralparticle 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 singlecopy of a positive-sense, single-stranded RNA genome. Humanantibodies raised against the DEN virion are mostly targeted at the andprMproteins.The virus is transmitted to humans by infectious bites of Aedesmosquitoes, in particular Ae. Aegyptibut also Ae. albopictus. Thesevectors are urban day-biting mosquitoes, such that insecticidetreatedbednets, which have been very important for malaria control, are ineffective [16]. Infected humans are the main carriersand multipliers of the virus, which then transmit DENV to uninfected mosquitoes for subsequent transmission. The geographicdistribution of dengue is determined in large part by the vector[17].

Overview of current efforts

Either Vaccines currently available and their limitations ORBiological feasibility for vaccine developmentIn December, 2015, the first dengue vaccine, Dengvaxia®(CYD-TDV) developed by Sanofi Pasteur, was licensed in Mexico [18]. Thevaccine was licensed in individuals 9–45 years living in endemicareas. CYD-TDV has since been licensed by several endemiccountries National Regulatory Authorities (NRA).CYD-TDV is a 3-dose live recombinant tetravalent dengue vac-cine administered on a 0/6/12 month schedule. It is based on theYF17D backbone, which is also the basis for the licensed JE vaccineIMOJEV [19]. CYD-TDV includes all three structural proteins, butbecause of the YF backbone, there are no dengue non-structuralproteins included. This vaccine has been evaluated in two largepivotal Phase 3 trials in 5 countries in Asia and 5 countries inLatin America, in participants aged 2–16 across the two trials[20,21] A strong caseor the feasibility of developing a dengue vaccine can be made basedon the assumed life-long homotypic immunity conferred by naturalinfection [22]. Due to the theoretical risk of immune enhancement,the dogma has been that a tetravalent vaccine inducing a balancedimmune response was needed [23]. The interim results of long-term follow up of CYD-TDV show these concerns to be relevant(though not confirmed), and ongoing/future development effortswill need to have practices in place to closely monitor for changesin risk, including in subgroups, and make all efforts to ensure thesafety of trial participants [24].

General approaches to vaccine development

MarketsMany dengue-endemic countries are middle-high incomeeconomies and provide a large market to drive development. Candidates under development are being designed primarily for use inendemic settings, which are predominantly low and middle incomecountries. For this reason and for easier implementation into immunization programs, there are efforts to minimize the number ofdoses needed, ideally for single-dose vaccines. One candidate vaccines have also been studied for having a low cost of goods [25]Live attenuated candidates under development have ongoing age de-escalation studieswith a target lower bound of 1 or 2 years due to interferencewith maternally derived antibodies and ADE and are both currentlybeing evaluated as single dose vaccines [26–29].

DNA vaccines

A tetravalent DNA vaccine candidate has been developed by theU.S. Centres for Disease Control and Prevention (CDC). Transfection of the recombinant plasmid vectors into cultured cells hasbeen shown to result in secretion of prM/E containing VLPs, whichhave an antigenic structure similar to DEN virions [30,31]. Immunogenicity of a tetravalent mixture of four monovalent DNA vaccineshas been evaluated in NHPs. The tetravalent vaccine was foundto stimulate a balanced immunity that lasted for 10 months andappeared to protect from viral challenge (J. Chang, personal communication), though the final results of the study have never beenpublished.In a prototype DENV-1 DNA vaccine (D1ME100) Phase 1 clinicaltrial in humans [32], a minority of participants developed anti-dengue neutralizing antibody responses but IFN _ T cell responseswere frequently detected. As a result, the U.S. Naval MedicalResearch Centre (NMRC) is pursuing an approach of adjuvantingthetetravalent dengue DNA vaccine, which is composed of equal partsof monovalent plasmid DNA vaccines encoding the PrM and E genes[33–36], with the proprietary adjuvant Vaxfectin®. Vaxfectin®isacationiclipid:neutral lipid combination [37].

Status of vaccine R&D activities

Preclinical pipeline

The preclinical pipeline for dengue vaccines includes both conventional as well as novel technological approaches, including recombinant subunit vaccines, DNA vaccines, VLP vaccines, virus-vectored vaccines, purified inactivated virus vaccines, live attenuated virus vaccines, heterologous prime-boost approaches ,and simultaneous administration with two technologically different vaccine candidates (Table 1) [47]. Approximately 20 candidates have been or are in the process of being evaluated in NHP models, with some expected to move soon into the clinic. Some novel approaches include a measles vaccine viral vector (Themis Bio-science) [48]

Clinical pipeline

In addition to CYD-TDV, two other tetravalent live recombinant vaccines, TV003/TV005 and DENVax, have just begun or are close tobeginning Phase 3 trials and do contain dengue virus non-structuralproteins for at least one serotype [38].TV003 and TV005 (which are identical except for the dosing levelof the dengue 2 component) were developed by the US NationalInstitutes of Health and are based on wild-type strains with geneticmutations to attenuate the virus [38]. Several monovalent candidates were first tested in Phase 1 trials to optimize each of thefour vaccine virus strains [39]. Vaccine virus serotypes 1, 3, and 4are based on complete viruses, while serotype 2 is a recombinantvirus based on the serotype 4 vaccine strain with the structuralproteins replaced by those of serotype 2. One dose of TV005elicits seroconversion rates over 90% against each serotype, and90% of flavivirus naive recipients mounted a tetravalent response[40]. A number of other candidates and approaches have been or are currently under evaluation in Phase 1 trials (Table 1) [41].These include a tetravalent purified inactivated vaccine (GSK) [42],a tetravalent recombinant subunit vaccine based on the denguewild-type premembrane and truncated envelope protein (Merck)[43,44], a monovalent plasmid DNA vaccine (US Navy MedicalResearchCenter) [45], and an inactivated vaccine/live attenuatedvaccine heterologous prime boost (Walter Reed Army Institute ofResearch) [46].

Vaccination benefits for naïve subject

The vaccination benefits over 10 years for 9-year-old childrenvaccinated before any dengue infection is presented Fig. 4a. In allcountries for these children, vaccination translated into a reduction of dengue cases despite the lower protection conferred by vaccinationand the potential of accelerated exposure to a second dengueinfection. This reduction, which results from a combination ofdirect and indirect protection, ranges from 32% for Malaysia to42% in Honduras. As expected the reduction was larger for all children vaccinated at age 9 years, i.e. seronegative and seropositive children. The results presented in Fig. 4b indicate reductions indengue cases ranging from 58% to 68%.

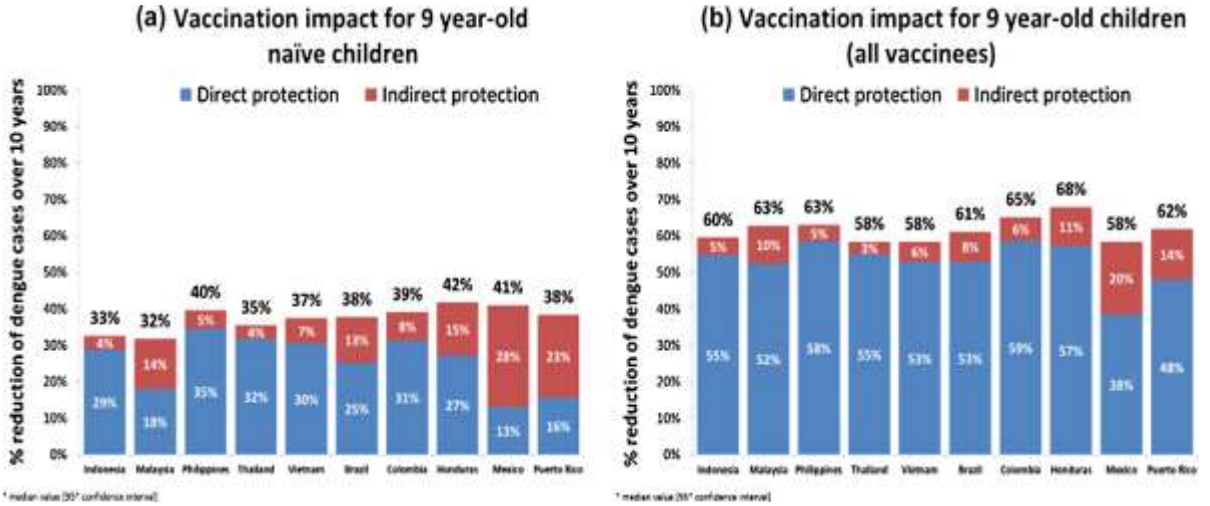

Fig. 4. Vaccination impact over 10 years for the first cohort of 9-year-old children receiving vaccination. (a) Children vaccinated when seronegative. (b) All vaccinate children. The vaccination program considered is a routine vaccination program at age 9 years combined with a catch-up campaign for those aged 10–17 years (8 catch-up cohorts). Vaccination coverage: 90%.

Conclusion

The World Health Organization recommended the use of mathematical models for vaccines. The analysis contributes to this effort. Routine vaccination fromage 9 years was found to have a significant impact on dengue cases across. The combination of routine vaccinationand catch-up campaigns provide an opportunity for a morerapid reduction in the dengue burden compared with routine vaccination alone. The reduction in the burden of dengue at the population level was obtained for scenarios of vaccine efficacy including the possibility of vaccine-induced cross-enhancement.Efforts to develop dengue vaccines have been ongoing for manyyears, but recent advances in vaccine science have greatly increased the technological options for dengue vaccine development. In parallel, molecular biology and systems biology permit more specific analysis of vaccine-induced immunogenicity and safety. However, possibly the most intriguing finding in relation to dengue vaccines over the past years comes from the first in class vaccine efficacy trial conducted with a yellow fever/dengue chimeric vac-cine candidate. The observed mismatch between protective efficacy and neutralizing titres demonstrates our limited understanding of protective immunity in dengue and the shortcomings of our diagnostic assays to measure vaccine induced immunity [50]. While the vaccine community awaits more detailed analysis of the dengue vaccine efficacy trials, interest has been renewed in evaluation of early stage candidates, both in NHPs and human challenge studies[51,52]

References

[1] Simmons CP, Farrar JJ, Nguyen VV, Wills B. Dengue, N Engl, J Med :2012; 366, pages:1423–32.

[2] Beatty ME, Beutels P, Meltzer MI, Shepard DS, Hombach J, Hutubessy R, et al, Healtheconomics of dengue: a systematic literature review and expert panel's assessment, Am J Trop Med Hyg 2011;84, pages: 473–88.

[3] Global alertand response impact ofdengue.Availableonline: ⟨http://www.who.int/csr/disease/dengue/impact/en/⟩, (accessed27.07.15).

[4]Murray,N.E.,Quam,M.B.,WilderSmith,A.,2013.Epidemiologyofdengue,past, present andfutureprospects.Clin.Epidemiol.5, pages: 299–309.

[5] Wilder-Smith,A.,2012.Dengueinfectionsintravellers.Paediatr.Int.Child.Health 32 (s1),pages :28–32.

[6] Semenza, J.C., Sudre, B., Miniota, J., Rossi, M., Hu, W., Kossowsky, D., et al., 2014. International dispersal of dengue through air travel: Importation risk for Europe, PLoSNegl. Trop. Dis. 8 (12), e3278.

[7] Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al, Theglobal distribution and burden of dengue. Nature 2013;496 (7446),pages: 504–7.

[8] Achee NL, Gould F, Perkins TA, Reiner Jr RC, Morrison AC, Ritchie SA, et al. Acriticalassessment of vector control for dengue prevention. PLoSNeglTropDis 2015;9(5):e0003655.

[9] Capeding MR, Tran NH, Hadinegoro SR, Ismail HI, Chotpitayasunondh T, ChuaMN, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine inhealthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet 2014;384(9951) pages:1358–65.
[10] Villar L, Dayan GH, Arredondo-Garcia JL, Rivera DM, Cunha R, Deseda C, et al.Efficacy of a tetravalent dengue vaccine in children in Latin America,NEnglJMed 2015;372(2) pages:113–23.
[11] Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, Deseda C, Chotpitaya-sunondh T, Dietze R, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease, N Engl J Med 2015;373(13) pages:1195–206.
[12] Simmons CP. A candidate dengue vaccine walks a tightrope. N Engl J Med2015;373(13) pages:1263–4.
[13] Pasteur S. New England Journal of Medicine publishes new analysesconfirming that Sanofi Pasteur's vaccine candidate safely protects pre-adolescents to adults against dengue; 2015. Lyon, France.
[14] Schmitz J, Roehrig J, Barrett A, Hombach J. Next generation denguevaccines: a review of candidates in preclinical development Vaccine ,2011;29(42) pages:7276–84.
[15] Guzman MG, Harris E. Dengue. Lancet 2015;385 pages :453–65.
[16] Achee NL, Gould F, Perkins TA, Reiner Jr RC, Morrison AC, Ritchie SA, et al. Acritical assessment of vector control for dengue prevention. PLoSNegl Trop Dis2015;9:e0003655.
[17] Kraemer MU, Sinka ME, Duda KA, Mylne AQ, Shearer FM, Barker CM, et al. Theglobal distribution of the arbovirus vectors Aedesaegypti and Ae. albopictus.Elife 2015;4:e08347.
[18] Comisión Federal para la Protección contra RiesgosSanitarios. MÉXICOAPRUEBA LA PRIMERA VACUNA CONTRA EL VIRUS DEL DENGUE A NIVELMUNDIAL; 2015.
[19] Guy B, Guirakhoo F, Barban V, Higgs S, Monath TP, Lang J. Preclinical and clinicaldevelopment of YFV 17D-based chimeric vaccines against dengue, West Nileand Japanese encephalitis viruses. Vaccine 2010;28 pages:632–49.
[20] Capeding MR, Tran NH, Hadinegoro SR, Ismail HI, Chotpitayasunondh T, ChuaMN, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine inhealthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet 2014;384 pages :1358–65.
[21] Villar L, Dayan GH, Arredondo-Garcia JL, Rivera DM, Cunha R, Deseda C, et al.Efficacy of a tetravalent dengue vaccine in children in Latin America. N EnglJMed 2015;372 pages:113–23.
[22] Halstead SB, Identifying protective dengue vaccines: guide to mastering anempirical process. Vaccine 2013;31 pages:4501–7
[23] Flipse J, Smit JM. The complexity of a dengue vaccine: a review of the humanantibody response. PLoSNegl Trop Dis 2015;9:e0003749.
[24] Live Dengue Vaccines Technical Consultation Reporting GroupBentsi-EnchillAD, Schmitz J, Edelman R, Durbin A, Roehrig JT, et al. Long-term safety assess-ment of live attenuated tetravalent dengue vaccines: deliberations from a WHOtechnical consultation. Vaccine 2013;31 pages :2603–9.
[25] Mahoney RT, Francis DP, Frazatti-Gallina NM, Precioso AR, Raw I, WatlerP,et
al. Cost of production of live attenuated dengue vaccines: a case study of theInstitutoButantan, Sao Paulo, Brazil. Vaccine 2012;30 pages :4892–6.
[26] ClinicalTrials.gov. Safety and immunogenicity of different schedules of Takeda'sTetravalent Dengue Vaccine Candidate (TDV) in healthy participants; 2015.
[27] Clinicaltrials.gov. Safety and immunogenicity with two different serotype 2potencies of Tetravalent Dengue Vaccine (TDV) in adults in Singapore; 2015.
[28] Clinicaltrials.gov. Evaluating the safety of and immune response to a denguevaccine (TV003) in healthy adults, adolescents, and children in Thailand; 2015.
[29] Clinicaltrials.gov. Phase III trial to evaluate efficacy and safety of a tetravalentdenguevaccine ; 2015
[30] Chang GJ, Hunt AR, Holmes DA, Springfield T, Chiueh TS, Roehrig JT, et al.Enhancing biosynthesis and secretion of premembrane and envelope proteinsbythechimeric plasmid of dengue virus type 2 and Japanese encephalitisvirus. Virology 2003;306(1) pages :170–80.
[31] Purdy DE, Chang GJ, Secretion of noninfectious dengue virus-like particlesand identification of amino acids in the stem region involved in intracellularretention of envelope protein. Virology 2005;333(2) pages :239–50.
[32] Beckett CG, Tjaden J, Burgess T, Danko JR, Tamminga C, Simmons M, et al.Evaluation of a prototype dengue-1 DNA vaccine in a Phase 1 clinical trial.Vaccine 2011;29(5) pages :960–8.
[33] Raviprakash K, Porter KR, Kochel TJ, Ewing D, Simmons M, Phillips I, et al.Dengue virus type 1 DNA vaccine induces protective immune responses inrhesus macaques. J Gen Virol 2000;81(Pt 7) pages :1659–67.

[34] Raviprakash K, Marques E, Ewing D, Lu Y, Phillips I, Porter KR, et al. Synergis-tic neutralizing antibody response to a dengue virus type 2 DNA vaccine byincorporation of lysosome-associated membrane protein sequences and useof plasmid expressing GM-CSF. Virology 2001;290(1) pages :74–82.
[35] Blair PJ, Kochel TJ, Raviprakash K, Guevara C, Salazar M, Wu SJ, et al. Evaluationof immunity and protective efficacy of a dengue-3 pre-membrane and enve-lope DNA vaccine in Aotusnancymae monkeys, Vaccine 2006;24(9) pages :1427–32.
[36] Lu Y, Raviprakash K, Leao IC, Chikhlikar PR, Ewing D, Anwar A, et al. Dengue2 PreM-E/LAMP chimera targeted to the MHC class II compartment elicitslong-lasting neutralizing antibodies. Vaccine 2003;21(17–18) pages :2178–89.
[37] Sullivan SM, Doukas J, Hartikka J, Smith L, Rolland A. Vaxfectin: a versatileadjuvant for plasmid DNA- and protein-based vaccines. Expert OpinDrugDeliv 2010;7(12) pages :1433–46.
[38] Schwartz LM, Halloran ME, Durbin AP, LonginiJr IM. The dengue vac-cine pipeline: implications for the future of dengue control. Vaccine2015;33:3293–8
[39] Durbin AP, Kirkpatrick BD, Pierce KK, Schmidt AC, Whitehead SS. Developmentand clinical evaluation of multiple investigational monovalent DENV vaccinesto identify components for inclusion in a live attenuated tetravalent DENVvaccine. Vaccine 2011;29 pages :7242–50.
[40] Kirkpatrick BD, Durbin AP, Pierce KK, Carmolli MP, Tibery CM, Grier PL, etal.Robust and balanced immune responses to all 4 dengue virus serotypes fol-lowing administration of a single dose of a live attenuated tetravalent denguevaccine to healthy, flavivirus-naive adults. J Infect Dis 2015;212(5) pages :702–10.
[41] Schwartz LM, Halloran ME, Durbin AP, LonginiJr IM. The dengue vac-cine pipeline: implications for the future of dengue control. Vaccine2015;33 pages :3293–8.
[42] Martinez LJ, Lin L, Blaylock JM, Lyons AG, Bauer KM, De La Barrera R, et al. Safetyand immunogenicity of a dengue virus serotype-1 purified-inactivated vaccine:results of a phase 1 clinical trial. Am J Trop Med Hyg 2015;93(3) pages :454–60.
[43] Coller BA, Clements DE, Bett AJ, Sagar SL, TerMeulen JH. The development ofrecombinant subunit envelope-based vaccines to protect against dengue virusinduced disease. Vaccine 2011;29 pages :7267–75.
[44] Govindarajan D, Meschino S, Guan L, Clements DE, TerMeulen JH, CasimiroDR, et al. Preclinical development of a dengue tetravalent recombinant sub-unit vaccine: immunogenicity and protective efficacy in nonhuman primates.Vaccine 2015;33(33) pages :4105–16.
[45] Beckett CG, Tjaden J, Burgess T, Danko JR, Tamminga C, Simmons M, et al. Eval-uation of a prototype dengue-1 DNA vaccine in a phase 1 clinical trial. Vaccine2011;29 pages :960–8.
[46] Clinicaltrials.gov. TDENV PIV and LAV dengue prime-boost strategy; 2015.
[47] Vannice KS, Roehrig JT, Hombach J. Next generation dengue vaccines: a reviewof the preclinical development pipeline. Vaccine 2015;33(50) pages :7091–9.
[48] Brandler S, Ruffie C, Najburg V, Frenkiel MP, Bedouelle H, Despres P, et al.Pediatric measles vaccine expressing a dengue tetravalent antigen elicitsneutralizing antibodies against all four dengue viruses. Vaccine 2010;28 pages :6730–9.
[49] Group W-VDVM. Assessing the potential of a candidate dengue vaccine with mathematicalmodeling. PLoSNegl Trop Dis 2012;6.
[50] Sirivichayakul C, Sabchareon A, Limkittikul K, Yoksan S. Plaque reductionneutralization antibody test does not accurately predict protection againstdengue infection in Ratchaburi cohort, Thailand. Virol J 2014;11:48.
[51] Cassetti MC, Thomas SJ, Dengue human infection model: introduction. J InfectDis 2014;209(Suppl. 2):S37–9.
[52] Halstead SB, Identifying protective dengue vaccines: guide to mastering anempirical process. Vaccine 2013;31(41) pages :4501–7.

How to cite this article
Goud P., Pathan J.K., Malviya S. and Kharia A. (2016). The recent development of dengue vaccination. *Int. J. Pharm. Life Sci.*, 7(12):5354-5359.
Source of Support: Nil; Conflict of Interest: None declared

Received: 10.11.16; Revised: 29.11.16; Accepted: 15.12.16