INNOVATION IMPARTING LASTING
IMMUNITY AGAINST

JAPANESE ENCEPHALITIS

JENVAC®

VERO-CELL DERIVED | INACTIVATED | PURIFIED
WORLD-CLASS

ESCALATING DISEASE BURDEN - UNPRECEDENTED SPREAD

- States affected by Japanese Encephalitis
- Emergence of G1 & its subtypes - a serious concern

REFERENCE

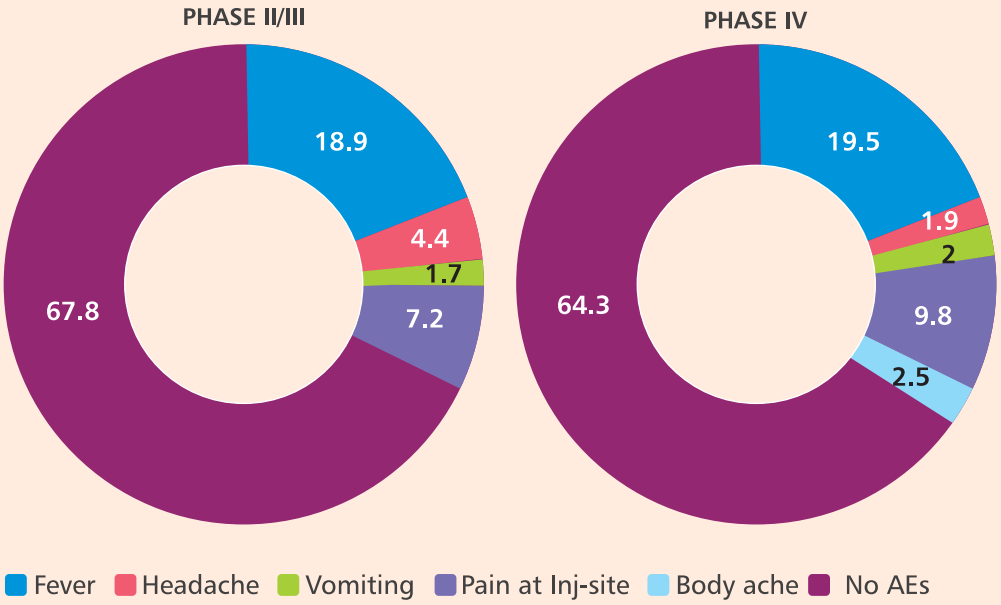
Japanese Encephalitis: A Brief Review on Indian Perspectives. Open Virol J. 2018 Aug 31; 12: 121-130.

WORLD'S 1st BIOREACTOR TECHNOLOGY FOR JENVAC®

Key Features -

- Fully-integrated, single-use 500+ bioreactor with disposable, pre-installed calibrated probes.
- Predictable scalability from R&D to manufacturing.
- Compact, high cell-density, fixed-bed bioreactor provides -
  - Increase in Yield vs. Traditional Approaches
  - Batch-to-Batch Consistency
  - High Antigen Purity

PROVEN SAFETY - PHASE II/III & PHASE IV STUDIES



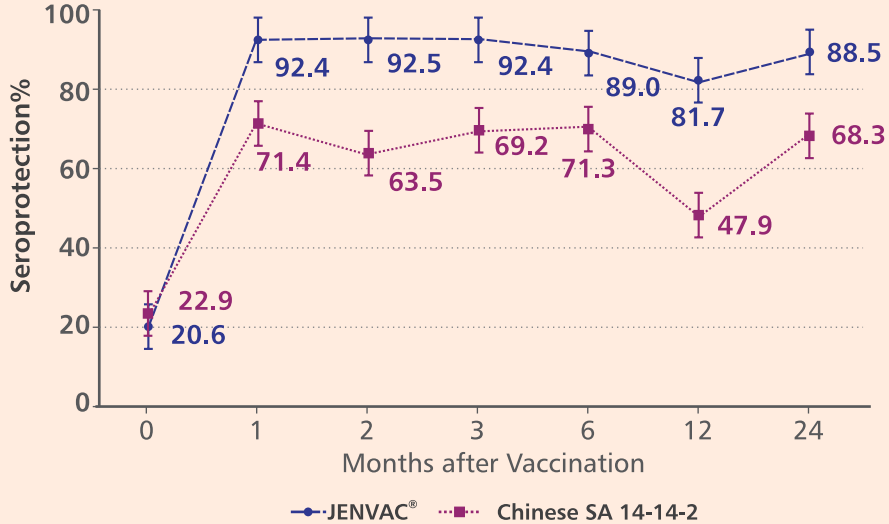
Proven Long-Term Immunogenicity - Phase II/III Single-Dose Study

		Seroprotection % (95% CI)
JENVAC®	12 Months	81.8 (65.7, 97.9)
	24 Months	85.7 (59.8, 111.7)
Chinese SA 14-14-2	12 Months	44.4 (11.9, 76.9)
	24 Months	50.0 (1.0, 99.0)

Excellent seroprotection with one dose (~96%) post 28 days in Phase III study[1]

1. Anit Singh, Monjori Mitra, Gadey Sampath, P. Venugopal, J. Venkateswara Rao, B. Krishnamurthy, Mukesh Kumar Gupta, S. Sri Krishna, B. Sudhakar, N. Bhuvaneswara Rao, Yashpal Kaushik, K. Gopinathan, Nagendra R. Hegde, Milind M. Gore, V. Krishna Mohan, and Krishna M. Ella. A Japanese Encephalitis Vaccine From India Induces Durable and Cross-protective Immunity Against Temporally and Spatially Wide-ranging Global Field Strains. J Infect Dis. 2015 Sep 1;212(5):715-25. doi: 10.1093/infdis/jiv023. Epub 2015 Jan 18.

Seroprotection of JENVAC® vs. Chinese SA 14-14-2 Phase IV Clinical Trial[2]

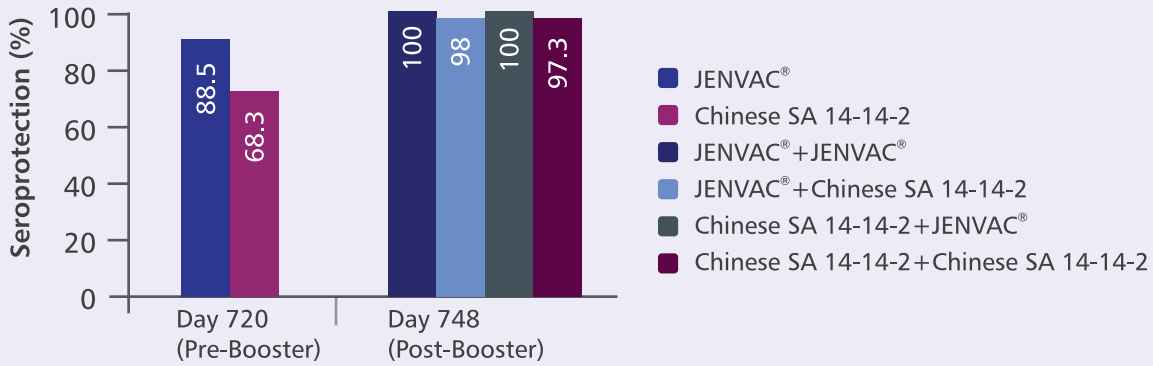


PROVEN BOOSTER DOSE & INTERCHANGEABILITY STUDY[2]

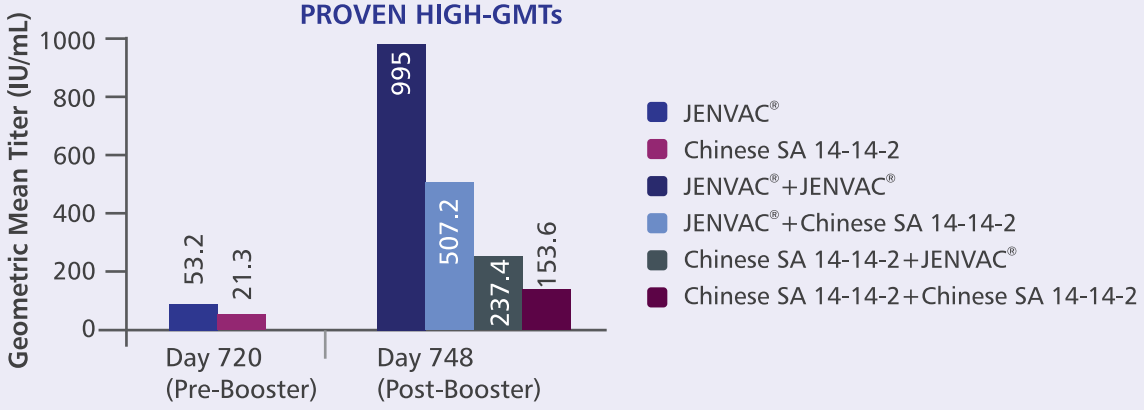
Superior boosting after two years of primary dose (Day 720).
Proven interchangeability post booster with Chinese SA 14-14-2.

	Prime Dose	Booster Dose
a)	JENVAC®	JENVAC®
b)	JENVAC®	Chinese SA 14-14-2
c)	Chinese SA 14-14-2	JENVAC®
d)	Chinese SA 14-14-2	Chinese SA 14-14-2

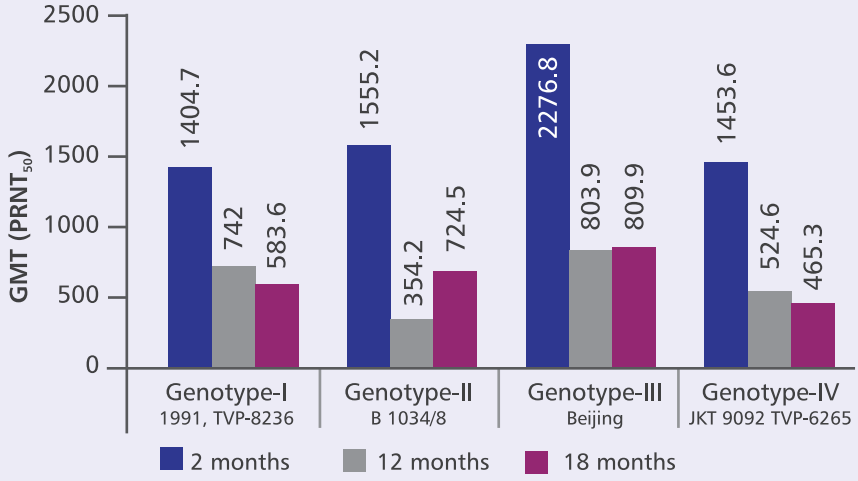
PROVEN LONG-TERM SEROPROTECTION



PROVEN HIGH-GMTs



PROVEN CROSS PROTECTION AGAINST G1-G4



- Proven cross protection against currently circulating strains of all major Genotypes (G1-G4).
- High GMTs against all Genotypes.
- Proven long-term immunogenicity against all Genotypes.

2.Vadrevu KM, Potula V, Khalatkar V, Mahantshetty NS, Shah A, Ella R. Persistence of Immune Responses With an Inactivated Japanese Encephalitis Single-Dose Vaccine, JENVAC and Interchangeability With a Live-Attenuated Vaccine. J Infect Dis. 2020 Oct 1;222(9):1478-1487. doi: 10.1093/infdis/jiz672. PMID: 31858116; PMCID: PMC7529014.

SALIENT FEATURES OF JENVAC®

- JE (JEV821564XY, thermostable) strain isolated from JE infected encephalitis patient.
- Produced under Public Private Partnership model with National Institute of Virology, Pune.
- World's 1st JE vaccine produced using Bioreactor Technology.
- Single-dose JENVAC® assures effective priming & 100% vaccine uptake.
- Proven cross protection against JEV G1 to G4, including subtypes of G1.
- Single-dose JENVAC®, an effective tool in minimizing 2nd dose drop-outs.
- Extensive clinical trials (Phase I to IV), excellent safety & long-term protection across age groups ≥1 year.
- No risk of residual/accidental neurovirulence.
- Long shelf-life of 3 years confers excellent stability.
- Proven interchangeability with Live Chinese SA 14-14-2 JE vaccine.

Comparison of Indigenous JENVAC® Vs. Chinese SA 14-14-2

Parameters	JENVAC®	Live Attenuated Vaccine (LAV)
Type of vaccine	Inactivated	Live
Cell substrate	Vero cells	Primary Hamster Kidney Cells
Posology	Single primary dose	Two primary doses
Safety	Excellent	Moderate
Immunogenicity	Excellent	Low
Long term protection	Excellent	Low
Cross protection	G1-G4 & Subtypes of G1	No data available
Interchangeability	Excellent	Modest

SINGLE DOSE JENVAC®

- Seroprotection, Seroconversion & GMTs, across four clinical trials involving ~1250 subjects at multiple sites across India, demonstrate superior immunogenicity & protection conferred by JENVAC® than live attenuated Chinese SA 14-14-2.
- JENVAC® offers long-term seroprotection with a Single Dose primary series.
- Excellent immune response elicited by a JENVAC® booster dose (post two years of primary dose), establishing an appropriate time for a booster.

PUBLICATIONS

Journal of Infectious Diseases Advance Access published February 23, 2015

MAJOR ARTICLE

A Japanese Encephalitis Vaccine From India Induces Durable and Cross-protective Immunity Against Temporally and Spatially Wide-ranging Global Field Strains

Anit Singh,[1] Monjori Mitra,[5] Gadey Sampath,[2] P. Venugopal,[6] J. Venkateswara Rao,[7] B. Krishnamurthy,[8] Mukesh Kumar Gupta,[9] S. Sri Krishna,[3] B. Sudhakar,[10] N. Bhuvaneswara Rao,[11] Yashpal Kaushik,[1] K. Gopinathan,[1] Nagendra R. Hegde,[4] Milind M. Gore,[12] V. Krishna Mohan,[1] and Krishna M. Ella[1]

The Journal of Infectious Diseases

MAJOR ARTICLE

Persistence of Immune Responses With an Inactivated Japanese Encephalitis Single-Dose Vaccine, JENVAC and Interchangeability With a Live-Attenuated Vaccine

Krishna Mohan Vadrevu,[1] Venugopal Potula,[2] Vasant Khalatkar,[3] Niranjana S. Mahantshetty,[4] Atish Shah[5], and Raches Ella[1]

[1]Bharat Biotech International Limited, Genome Valley, Shameerpet, Hyderabad, India, [2]King George Hospital, Maharanipeta, Vishakhapatnam, India, [3]Colours Children Hospital, Jasleen, Pachsheel Square, Nagpur, India [4]KLE Hospital, Belgavi, India, [5]Sangini Hospital, Ahmedabad, India

PATENTS

Patent No: 4135/CHE/2013 - India.
PCT/IN2014/000585 - International

ABRIDGED PRESCRIBING INFORMATION

Posology and method of administration: JENVAC® is administered intramuscularly into the deltoid region of upper arm for adults and anterolateral region of thigh for children. Do not administer intravenously, subcutaneously or intradermally. **Dosage & schedule:** The primary vaccination consists of a single dose of 0.5 mL. If the vaccine was administered more than 1 year ago, a booster dose may be given prior to potential re-exposure or visiting to endemic area. It is recommended that the vaccinee who received first dose of JENVAC® should receive their booster dose of vaccination with JENVAC®. The vaccine has to be administered by a qualified healthcare professional. Shake the vaccine container well to obtain uniform suspension before administration. **Contraindications:** Vaccine must not be given to individuals with known or suspected hypersensitivity to the components of the vaccine. Severe allergic reaction (e.g. anaphylaxis) after a previous dose of JENVAC® is a contraindication to administration of next (booster) dose. Administration must be postponed in persons with fever or other conditions as deemed necessary by the administering physician. **Special warning/precaution:** Do not administer intravenously, intradermally, or subcutaneously. Do not administer if particulate matter remains following shaking or if discoloration is observed.Like with all other vaccines, supervision and appropriate medical treatment should always be available for treatment of any anaphylactic reactions that may occur after immunization. JENVAC® will not protect against encephalitis caused by other micro-organisms. Interaction with other medicinal products and other forms of interaction: For concomitant administration of other injectable product, use different injection sites and separate syringes. JENVAC® should not be mixed with any other vaccine or medicinal product, because the interactions with other vaccines or medicinal products have not been established. **Pregnancy and lactation:** Safety and efficacy have not been established in pregnant women and in nursing mothers. It is not known whether this vaccine is excreted in human milk. **Effect on ability to drive and use machines:** No studies on the effect of JENVAC® on the ability to drive and use machines have been performed. For use only of a Registered Medical Practitioner or Hospital or Laboratory **Undesirable effects:** The safety of JENVAC® vaccine was established in controlled clinical trials in healthy volunteers in comparison with a licensed JE vaccine. General adverse events such as fever headache, body ache and local adverse events such as pain, redness and swelling at the injection site were the frequently reported adverse events after administration of JENVAC®. They usually occurred within first 48 hours after vaccination and dissipate within 2 days.Within each system organ class, the adverse reactions are ranked under headings of frequency using the following convention: Very common : ≥10% Common : ≥1% and <10% Uncommon : ≥0.1% and <1% Rare : ≥0.01% and <0.1% Very rare :<0.01% Using above convention, the reported adverse events were: Very common: Fever, Common: Headache, Bodyache, Pain, Swelling and Redness at injection site Uncommon: Nausea, Vomiting, Diarrhea, Cold, Cough, Myalgia **Overdose:** No case of overdose with JENVAC® has been reported. **Pharmacological properties:** Encephalitis vaccines, ATC code: J07BA02 Japanese Encephalitis is a disease caused by mosquito-bome JE virus. JENVAC® is a vero-cell based purified inactivated vaccine that is known to act by inducing antibodies that neutralize live JEV. Clinical studies: In a phase I study, the safety and immunogenicity of BBIL's JENVAC® vaccine was established in healthy adult volunteers and the development proceeded to phase II/III study. The phase II/III, randomized, single blinded, active controlled study was conducted to evaluate the immunogenicity and safety of JENVAC® vs. Chinese SA 14-14-2 (live attenuated JE vaccine) in healthy volunteers. In this study, proportion of subjects achieving sero-protection after a single dose of respective vaccine, was significantly higher in JENVAC® treatment arm (98.7%) compared to that in the Chinese SA 14-14-2 arm (77.6%), 28 days post vaccination. Similarly, a phase IV, open labeled, comparative, randomized, active controlled study was conducted to evaluate the immunogenicity and safety of a single dose of JENVAC® vs. Chinese SA 14-14-2 vaccine in healthy volunteers. While the proportion of subjects being sero-negative or sero-positive for JE antibodies was similar in both treatment groups at the baseline, proportion of subjects achieving sero-protection was significantly higher in the JENVAC® treatment arm (92.4%) compared to that in the Chinese SA 14-14-2 arm (71.4%), 4 weeks after vaccination. Further, the higher sero-protection rate was persistent till 1 year of follow up among the subjects receiving JENVAC® vaccine;81.7% vs 47.9% (p = 0.0001). **Pharmacokinetic properties:** Evaluation of pharmacokinetic properties is not required for vaccines. Pre- Clinical safety data & Pre-clinical toxicology studies were carried out in lab animals where the vaccine did not elicit any toxic findings. Shelf life: The expiry date of the vaccine is indicated on the label and carton of the product.

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