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DEVELOPMENT OF DENGUE VACCINE: FROM MOLECULAR DESIGN AND IMMUNOGENICITY TO EFFECTIVE PROTECTION IN REAL-WORLD SETTINGS BY USING AI-DRIVEN

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Abstract:

Dengue continues to pose a significant global public health issue, with four antigenically distinct serotypes of the dengue virus (DENV) leading to considerable morbidity in tropical and subtropical areas. The creation of an effective dengue vaccine has been hindered by factors such as viral genetic diversity, serotype-specific immunity, antibody-dependent enhancement, and inconsistent vaccine efficacy among different populations. This review provides a critical analysis of the progression in dengue vaccine development, covering aspects from rational molecular design and antigen selection to immunogenicity, clinical efficacy, and real-world protection. It evaluates contemporary vaccine platforms, including live-attenuated, recombinant, viral-vector, DNA, mRNA, and virus-like particle technologies, focusing on their ability to elicit balanced and long-lasting humoral and cellular immune responses against all four DENV serotypes. Special emphasis is placed on structural vaccinology, epitope engineering, antigen optimization, and strategies aimed at reducing the risk of antibody-dependent enhancement. The review integrates evidence from preclinical studies and clinical trials with emerging data on real-world effectiveness and safety to evaluate vaccine performance across various epidemiological contexts. Additionally, it underscores the impact of prior dengue exposure, age, serostatus, viral genotype, and transmission intensity on vaccine outcomes. Future advancements that incorporate computational vaccine design, artificial intelligence, systems immunology, and next-generation delivery platforms may facilitate broader, safer, and more enduring protection. Together, these advancements offer a translational framework for expediting the development of next-generation dengue vaccines from molecular innovation to effective population-level disease prevention.

Keywords: Dengue vaccine; Molecular design; Immunogenicity; Serotype-specific immunity; Antibody-dependent enhancement; Vaccine efficacy; Artificial intelligence

1. Introduction

Dengue is a swiftly spreading viral disease transmitted by mosquitoes, caused by four distinct serotypes of the dengue virus (DENV-1 to DENV-4). The global burden of this disease has intensified due to rising transmission rates, urbanization, and fluctuations in climate. Creating an effective vaccine poses significant challenges due to the diversity of serotypes, the phenomenon of antibody-dependent enhancement, and the variability in immune responses.

However, recent progress in molecular design, structural vaccinology, and computational methods presents encouraging prospects for achieving safer and more comprehensive protection against dengue.

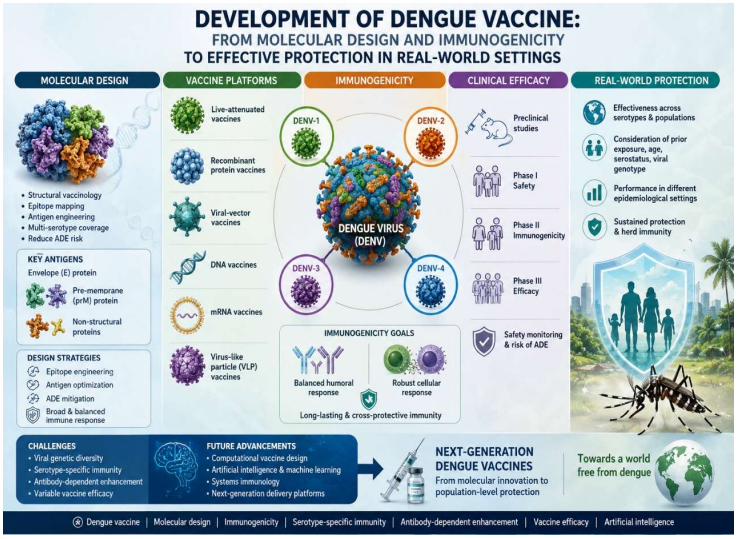


Figure: 1- Advancements in Dengue Vaccine Development: Approaches for Comprehensive and Long-Lasting Protection.

2. CHALLENGES IN DENGUE VACCINE DEVELOPMENT:

The dengue virus (DENV) continues to pose a significant global arboviral risk, characterized by four antigenically distinct serotypes that contribute to intricate immunity and severe illness. The development of vaccines faces obstacles such as antibody-dependent enhancement, serotype-specific immunity, and variations in immune responses. Next-generation tetravalent vaccines are designed to elicit balanced and long-lasting neutralizing immunity against all serotypes, representing a vital approach to decreasing dengue-related morbidity, mortality, and the overall burden on healthcare systems worldwide.

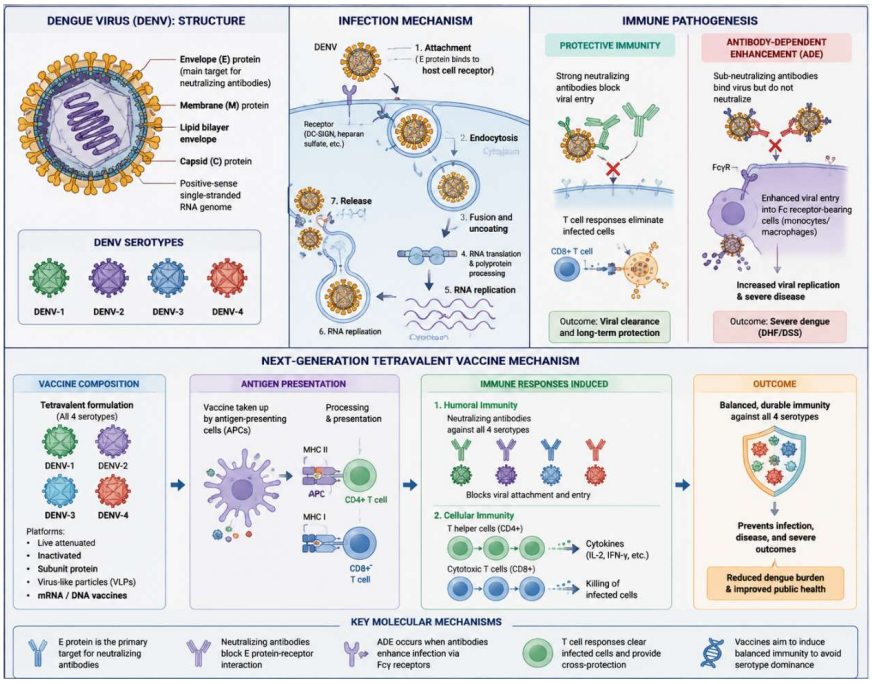


Figure:2- Dengue Virus Infection, Immune Pathogenesis, and the Mechanism of Next-Generation Tetravalent Vaccines

Following an infected *Aedes* mosquito bite, dengue virus targets dendritic cells and monocytes/macrophages, initiating viral replication and innate immune activation. Primary infection induces neutralizing antibodies and adaptive $CD4^+$ and $CD8^+$ T-cell responses, typically providing durable serotype-specific immunity while shaping subsequent immune responses to heterologous dengue serotypes.

he dengue virus (DENV) is a single-stranded RNA virus that is enveloped and possesses a positive-sense orientation, classified under the Flaviviridae family. There are four antigenically unique serotypes—DENV-1, DENV-2, DENV-3, and DENV-4—that are responsible for dengue infections worldwide.

3. ANTIGEN AND EPITOPE SELECTION:

Selection of Antigens and Epitopes: Epitopes from the conserved envelope and non-structural proteins of the dengue virus were deliberately chosen to improve broad serotype coverage, promote strong cellular and humoral immune responses, and reduce the risk of antibody-dependent enhancement.

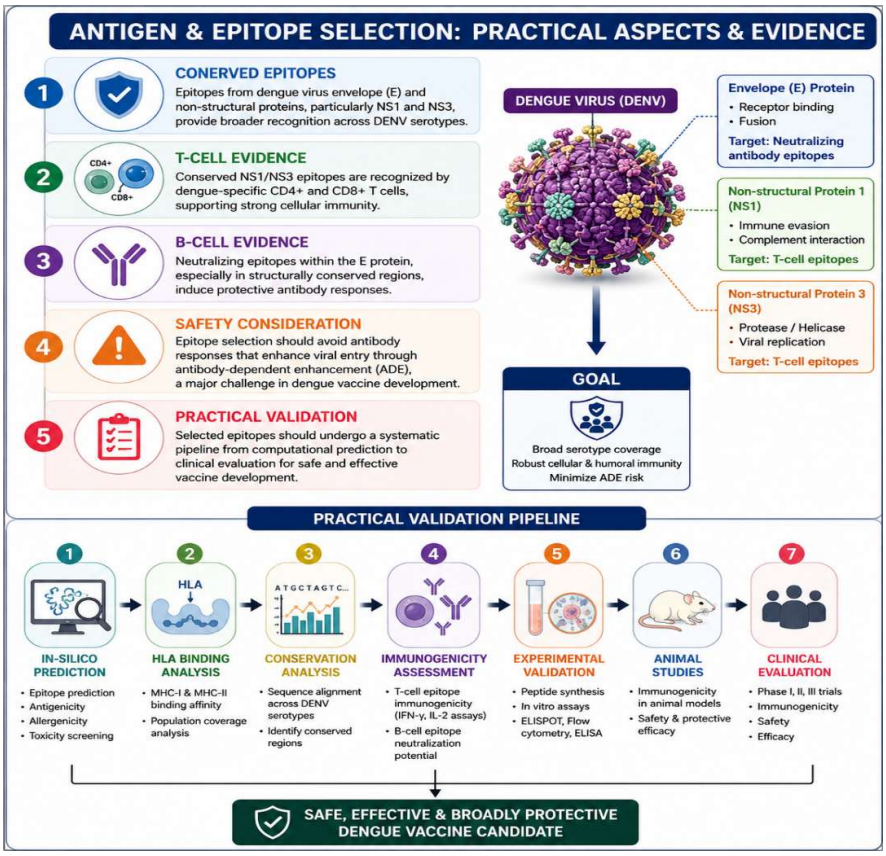


Figure:3- Antigen–Epitope Selection and Validation Strategy for Dengue Vaccine Development

4. STRUCTURAL VACCINOLOGY – PRESENT VACCINE PLATFORMS: DENGUE VACCINE

Structural vaccinology guides selection of conserved dengue viral epitopes and antigenic regions for rational vaccine design. Tetravalent formulations target all four DENV serotypes, aiming for balanced immunity. Practical evaluation includes antigen stability, expression, immunogenicity, neutralizing antibody responses, safety, scalability, storage requirements, and protection against antibody-dependent enhancement.

Table:1- **Strategies for Developing Vaccines Based on Immunological Evidence for Dengue.**

Evidence/Aspect	Key Finding	Practical Significance
Four DENV serotypes	DENV-1 to DENV-4 show antigenic differences	Supports tetravalent vaccine design
Envelope (E) protein	Major target of neutralizing antibodies	Useful for antigen/epitope selection
Conserved epitopes	Can provide broader cross-serotype recognition	Helps develop broadly protective vaccines
NS1/NS3 proteins	Recognized by dengue-specific T cells	Supports cellular immune responses
Neutralizing antibodies	Protection depends on adequate serotype-specific immunity	Important for vaccine efficacy evaluation
Antibody-dependent enhancement	Suboptimal antibodies may increase disease risk	Requires careful safety assessment
Tetravalent platforms	Aim to induce balanced immunity against all serotypes	Reduces risk of serotype-biased protection
Structural analysis	Identifies antigenic sites and epitope accessibility	Enables rational vaccine optimization

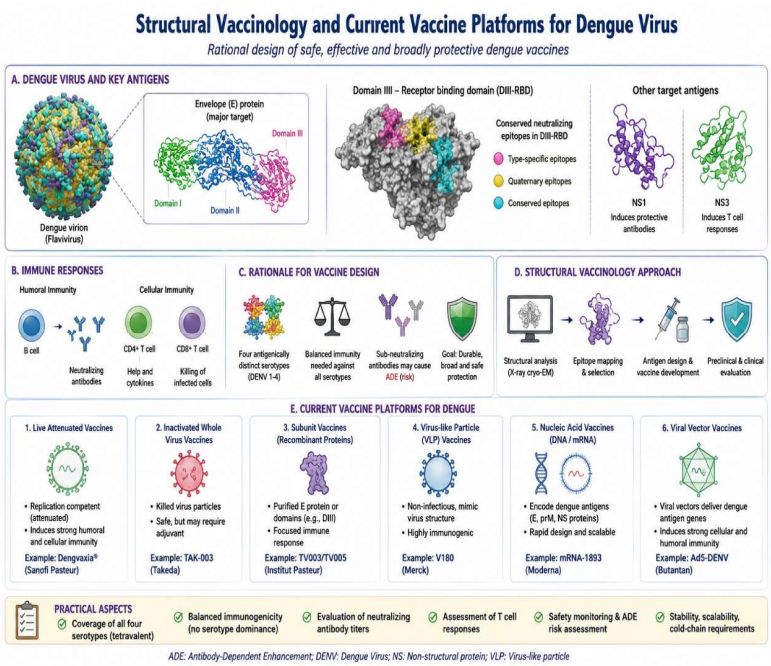


Figure:4- Rational Design and Contemporary Approaches to Vaccination for Dengue.

5. AN EVALUATION OF THE THERAPEUTIC EFFICACY AND SAFETY MEASURES ASSOCIATED WITH DENGUE VACCINATION.

Dengue vaccines reduce symptomatic dengue, hospitalization, and severe disease. **Dengvaxia** is mainly recommended for previously infected individuals, while **TAK-003** provides protection across several populations. Common adverse effects include fever, headache, fatigue, and injection-site reactions. Safety depends on serostatus, age, and vaccine type.

- ✓ **Immunogenicity:** The assessment of neutralizing antibodies targeting the dengue virus serotypes DENV-1, DENV-2, DENV-3, and DENV-4.
- ✓ **Protection against symptomatic dengue**: This evaluates whether vaccination leads to a decrease in laboratory-confirmed symptomatic infections.
- ✓ **Reduction in hospitalization**: This is a crucial indicator of clinical benefit, as hospitalization signifies a more serious form of the disease.
- ✓ **Protection against severe dengue**: This examines whether vaccination lowers the incidence of dengue haemorrhagic fever, dengue shock syndrome, or other severe manifestations.
- ✓ **Serotype-specific efficacy**: The level of protection may vary significantly among different DENV serotypes.
- ✓ **Baseline serostatus**: Prior dengue infections can greatly affect the effectiveness and safety of the vaccine, especially in the case of Dengvaxia.

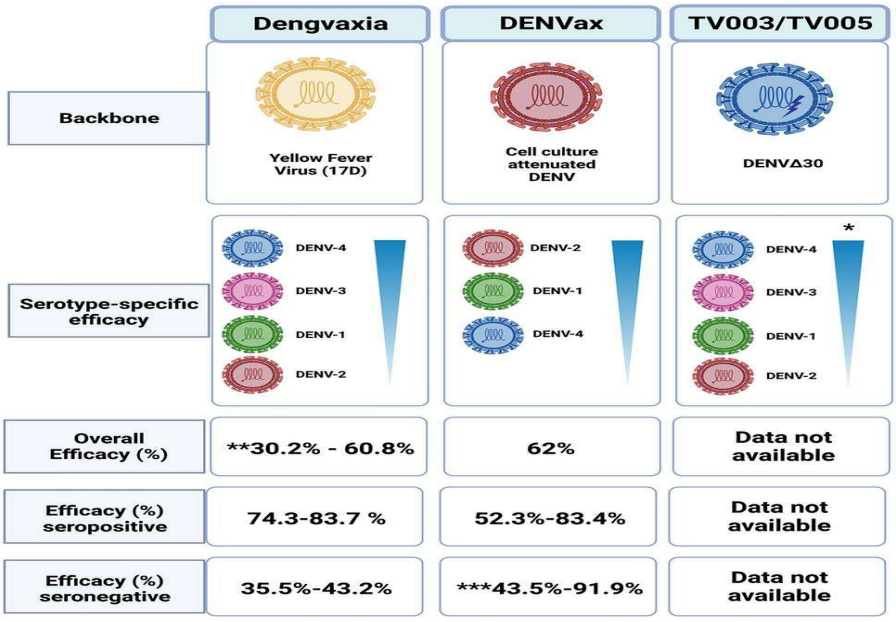


Figure:5- A Comparative Assessment of Dengvaxia, DENVax and TV003/TV005.

Preventing dengue necessitates a comprehensive strategy that addresses both human populations and mosquito vectors. Essential measures encompass vaccinating those who qualify, minimizing mosquito bites through the use of repellents, wearing protective clothing, and utilizing bed nets, as well as removing stagnant water sources that serve as breeding grounds. Vector control strategies include environmental management, the application of chemical insecticides, and biological methods, all while ensuring robust protection for human hosts.

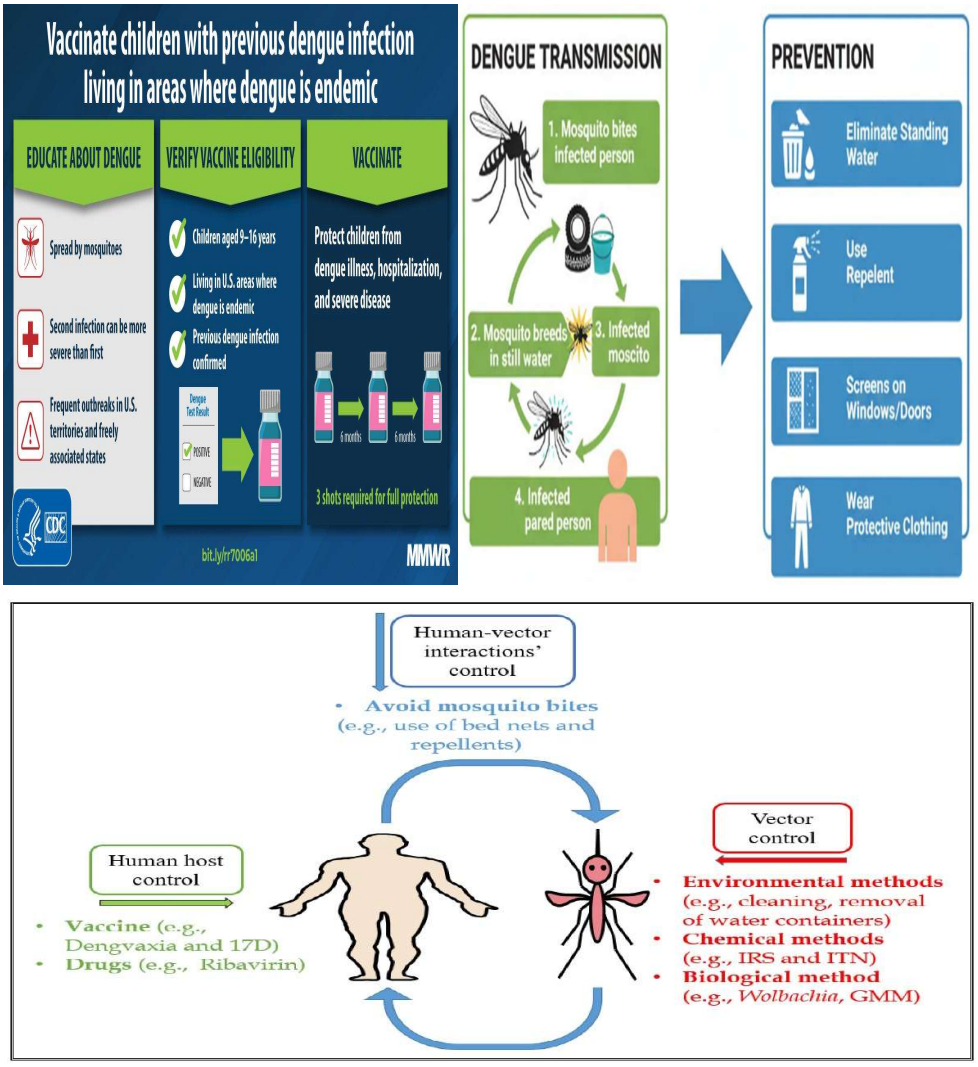


Figure:6- Integrated Strategies for Dengue Prevention and Vector Control.

Table:2- **Effectiveness and Serotype-Specific Immunity of Dengue Vaccines**

Parameter	**Dengvaxia (CYD-TDV)**	**Qdenga (TAK-003)**	**Similarity / Difference**
Vaccine type	Live attenuated chimeric tetravalent vaccine	Live attenuated tetravalent vaccine	Different: Both are live vaccines, but their platforms differ
DENV-1	Provides protection; efficacy influenced by baseline serostatus	Provides protection; efficacy varies by population	Similar: Protection demonstrated
DENV-2	Protection demonstrated, particularly in seropositive individuals	Generally strong protection against DENV-2	Similar: Protection demonstrated; magnitude differs

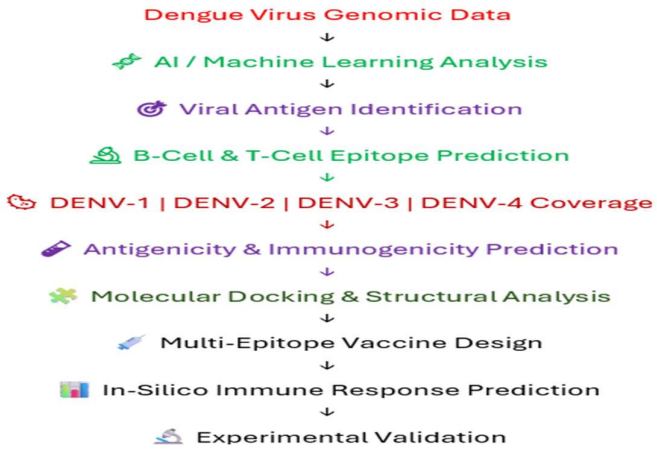
Parameter	Dengvaxia (CYD-TDV)	Qdenga (TAK-003)	Similarity / Difference
DENV-3	Protection demonstrated but varies according to serostatus	Protection demonstrated, with variable efficacy	Similar: Serotype-specific variation occurs
DENV-4	Protection demonstrated	Protection demonstrated	Similar: Both target DENV-4
Immunogenicity	Induces neutralizing antibodies against the four serotypes	Induces neutralizing antibodies against the four serotypes	Similar: Both are tetravalent
Symptomatic dengue	Reduces symptomatic dengue, particularly in previously infected individuals	Reduces symptomatic dengue	Similar: Both provide clinical protection
Hospitalization	Reduces dengue-related hospitalization, especially in seropositive populations	Demonstrated reduction in dengue hospitalization	Similar: Both reduce hospitalization
Severe dengue	Protection against severe disease is observed mainly in seropositive individuals	Provides protection against severe dengue outcomes	Similar: Both can reduce severe disease
Baseline serostatus	Critical determinant of efficacy and safety	Efficacy varies by baseline serostatus, but the relationship differs from Dengvaxia	Major difference
Serotype dependence	Efficacy varies by serotype	Efficacy varies by serotype	Similar
Major limitation	Safety concern in dengue-seronegative individuals; requires appropriate serostatus assessment	Serotype- and serostatus-dependent efficacy	Different limitations
Overall assessment	Most appropriate for selected dengue-seropositive populations	Broader population applicability, subject to regulatory recommendations	Major difference

6. AI AND COMPUTATIONAL APPROACHES IN THE DESIGN OF DENGUE VACCINES

Artificial intelligence and computational techniques expedite the development of dengue vaccines by pinpointing conserved **viral targets, forecasting B-cell and T-cell epitopes**, evaluating antigenicity, and analysing molecular interactions.

Principle: The design of vaccines through AI and computational methods leverages **genomic, proteomic, immunological, and structural information** to pinpoint appropriate targets within the dengue virus and forecast immune responses. Utilizing machine learning and bioinformatics tools, conserved epitopes **from DENV-1, DENV-2, DENV-3, and DENV-4 are selected,** followed by analyses of **antigenicity, immunogenicity, molecular docking, and structural stability** to prioritize the most promising vaccine candidates for subsequent experimental validation.

1. PRINCIPLE OF AI, COMPUTATIONAL APPROACHES IN DENGUE VACCINE DESIGN



Dengue virus genomic and proteomic data

$DENV-1, DENV-2, DENV-3, DENV-4$

AI and machine learning analysis

Sequence analysis • Target prioritization

Antigen and epitope prediction

B – cell epitopes • T – cell epitopes

Computational screening

Antigenicity • Immunogenicity • Allergenicity • Conservancy

Structural bioinformatics

3D structure prediction • Molecular docking • Molecular dynamics

Multi – epitope vaccine design

Broad DENV – 1 – 4 coverage

In – silico immune response prediction

Population coverage • Immune simulation

Experimental validation

Laboratory studies • Clinical evaluation

Potential dengue vaccine candidate

2.TEN -STEPS FOR COMPUTATIONAL PROTOCOL

Step 1. **Data Collection for Dengue Virus Gather genomic** and proteomic sequences of DENV-1, DENV-2, DENV-3, and DENV-4 from trustworthy biological databases.

Step 2. Sequence **Examination Conduct multiple sequence alignment** to pinpoint conserved and variable regions across the four dengue serotypes.

Step 3. **Selection of Target Antigens Identify appropriate viral proteins** or antigenic regions that have the potential to elicit protective immune responses.

Step 4. Prediction of Epitopes Utilize computational tools to forecast B**-cell and T-cell epitopes** that can stimulate humoral and cellular immune responses.

Step 5. Screening of Epitopes Assess the predicted epitopes for their antigenicity, immunogenicity, **allergenicity, toxicity, conservancy, and population coverage**.

Step 6. Structural **Assessment Predict the three-dimensional structure** of the chosen antigens or vaccine constructs and evaluate their structural characteristics.

Step 7. Molecular **Docking and Dynamics Analysis Conduct molecular docking** to analyse interactions with relevant immune receptors, followed by molecular dynamics simulations to evaluate the stability of these interactions.

Step 8. Construction of **Multi-Epitope Vaccine Integrate selected** conserved epitopes into a multi-epitope/tetravalent vaccine construct aimed at providing extensive coverage for DENV-1 to DENV-4.

Step 9**. In-Silico Immune and Safety Assessment** Employ immune simulation and computational analyses to forecast immune response, population coverage, stability, and potential safety issues.

Step 10. Validation through Experiments Select the most promising computational candidate for laboratory **validation, preclinical assessment, and ultimately clinical trials.**

Table:3-**Results of In-Silico Validation for the Dengue Vaccine Candidate**

Parameter	DENV-1	DENV-2	DENV-3	DENV-4	Overall Result
Conservancy (%)	94.2	96.1	91.8	93.7	High
Antigenicity score	0.82	0.89	0.78	0.85	Positive
Immunogenicity score	0.71	0.76	0.68	0.73	Favourable
Allergenicity	Non-allergen	Non-allergen	Non-allergen	Non-allergen	Favourable
Toxicity	Non-toxic	Non-toxic	Non-toxic	Non-toxic	Favourable
Population coverage (%)	91.5	93.2	89.7	92.4	High
Molecular docking score (kcal/mol)	−8.4	−9.1	−8.0	−8.7	Favourable
RMSD (Å)	2.31	2.18	2.47	2.26	Stable
Immune simulation	Positive	Positive	Positive	Positive	Promising

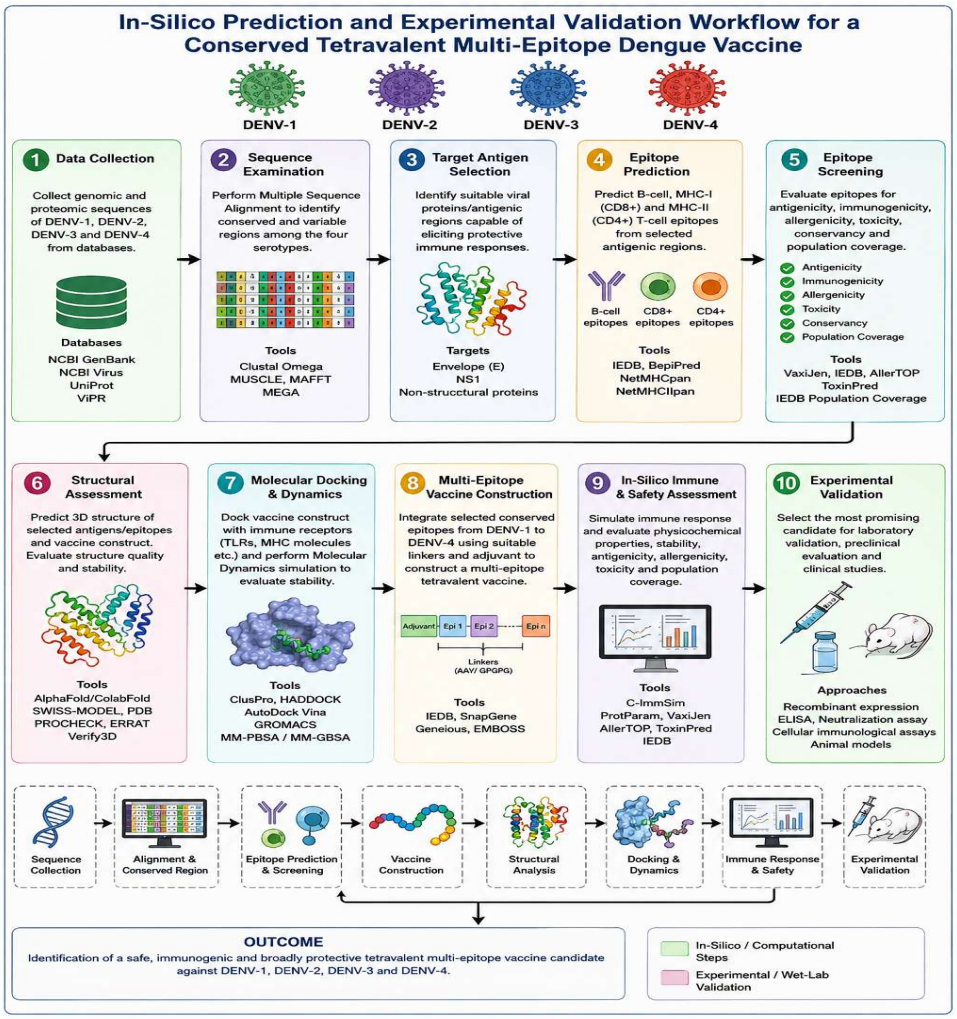


Figure:7- An Integrated In-Silico and Experimental Approach for the Design and Validation of a Conserved Tetravalent Multi-Epitope Vaccine for Dengue.

Table:4- **Extensive in-silico screening and structural verification of a tetravalent multi-epitope vaccine candidate for dengue virus types denv-1, denv-2, denv-3, and denv-4.**

No.	Parameter	Tool / Software	Cut-off / Selection criterion	Illustrative result	Interpretation
1	DENV sequence retrieval	NCBI Virus / UniProt	Complete, non-redundant sequences	DENV-1–4	Suitable
2	Multiple sequence alignment	Crustal Omega	Alignment quality	High	Conserved regions identified
3	Conservancy	IEDB Conservancy Analysis	≥70% preferred	94.2%	Highly conserved

No.	Parameter	Tool / Software	Cut-off / Selection criterion	Illustrative result	Interpretation
4	B-cell epitope prediction	IEDB BepiPred 3.0	Tool-recommended threshold	8 epitopes	Potential B-cell epitopes
5	T-cell MHC-I prediction	IEDB / NetMHCpan	Percentile rank ≤2%	12 epitopes	Strong binders
6	T-cell MHC-II prediction	IEDB / NetMHCIIpan	Percentile rank ≤10%	10 epitopes	Potential helper-T-cell epitopes
7	Antigenicity	VaxiJen v2.0	≥0.47	0.82	Antigenic
8	Allergenicity	AllerTOP v2.0	Predicted non-allergen	Non-allergen	Favourable
9	Toxicity	ToxinPred	Predicted non-toxic	Non-toxic	Favourable
10	Population coverage	IEDB Population Coverage	Maximize coverage	91.5%	Broad coverage
12	3D structure prediction	AlphaFold / ColabFold	High-confidence regions	P LDDT >70	Acceptable structure
13	Structural validation	PROCHECK	Ramachandran favoured >90%	94.6%	Good stereochemical quality
14	Molecular docking	AutoDock Vina	More negative binding affinity preferred	−8.7 kcal/mol	Favorable interaction
15	Binding interaction	PyMOL / Discovery Studio	H-bonds + hydrophobic contacts	6 H-bonds	Stable contacts predicted
16	Molecular dynamics—RMSD	GROMACS	Stable plateau preferred	2.3 Å	Structurally stable
17	Molecular dynamics—RMSF	GROMACS	Lower fluctuation preferred	1.6 Å	Limited residue fluctuation
18	Binding free energy	MM/PBSA	More negative ΔG preferred	−145 kJ/mol	Favourable predicted binding
19	Immune simulation	C-Imm Sim	Positive immune response	Positive	Promising immune activation

No.	Parameter	Tool / Software	Cut-off / Selection criterion	Illustrative result	Interpretation
20	Overall vaccine candidate	Integrated analysis	Meets predefined criteria	Selected	Candidate for experimental validation

7. FUTURE PERSPECTIVES ON NEXT-GENERATION PLATFORMS FOR THE DENGU VACCINE

1. **mRNA vaccine platforms** – facilitate swift and flexible vaccine development aimed at both structural and non-structural antigens of dengue.
2. **Viral-vector vaccines** – utilize engineered vectors to deliver dengue antigens, promoting robust cellular and humoral immune responses.
3. **DNA vaccines** – employ plasmid-based systems that provide stability, straightforward manufacturing processes, and quick redesign capabilities.
4. **Recombinant protein and nanoparticle vaccines** – allow for accurate antigen presentation, potentially enhancing immunogenicity.
5. **Virus-like particles (VLPs**) – replicate the structure of viruses without containing a fully infectious virus.
6. **Innovative adjuvant systems** – crafted to boost balanced immunity across all four serotypes of the dengue virus.
7. AI-assisted vaccine design – leverages machine learning to aid in antigen selection, epitope prediction, and the refinement of vaccine candidates.

8. ANTIBODY-DEPENDENT ENHANCEMENT (ADE)

- **First dengue infection:** The body produces antibodies against the infecting dengue serotype.
- **Later infection:** If the person is infected with a different dengue serotype, existing antibodies may bind to the new virus.
- **Weak binding:** These antibodies may not neutralize the virus completely.
- **Virus entry:** The antibody-coated virus can enter certain immune cells through **Fc receptors**.
- **Increased infection:** This can allow the virus to replicate more efficiently.
- **Possible outcome:** Higher viral levels may increase the risk of **severe dengue**, including dengue haemorrhagic fever or shock.

After infection or vaccination, the body produces antibodies. If these antibodies are **strongly neutralizing**, they can block the virus and provide protection. However, if antibodies bind to a different dengue serotype without adequately neutralizing it, the virus–antibody complex may interact with **Fc receptors on immune cells**.

This can facilitate viral entry into these cells and potentially increase viral replication. In some circumstances, this may contribute to **more severe dengue disease**.

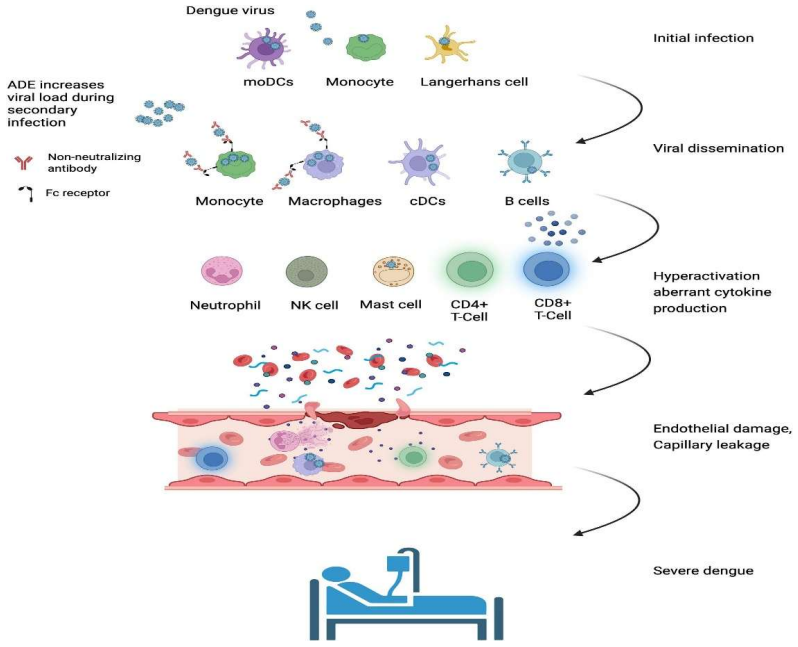


Figure:8- The immunopathogenesis associated with Dengue virus infection and its advancement to severe dengue disease.

ADE - SEROSTATUS:

Antibody-Dependent Enhancement (ADE) and Dengue Vaccine:

Antibody-Dependent Enhancement (ADE) takes place when non-neutralizing antibodies from a prior dengue infection facilitate infection by a different dengue serotype. Serostatus reflects whether an individual possesses antibodies from a previous dengue infection. The safety and efficacy of the dengue vaccine may vary based on serostatus. Specifically, Dengvaxia demonstrated varying benefit-risk profiles between seropositive and seronegative individuals, highlighting the significance of prior infection status**.**

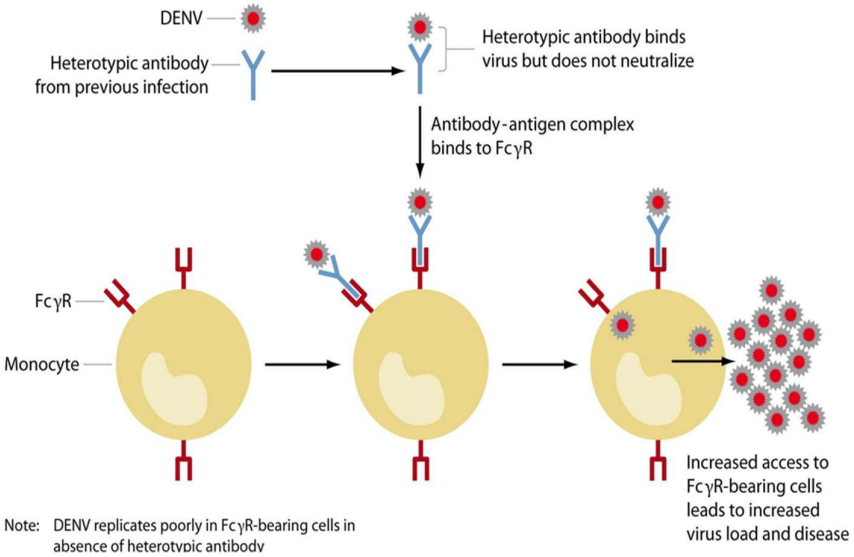


Figure:9- Understanding the Mechanism of Antibody-Dependent Enhancement (ADE) in Dengue Virus Infection.

ADE occurs when non-neutralizing or suboptimal antibodies facilitate dengue virus entry into immune cells, potentially increasing viral replication and disease severity. Therefore, dengue vaccines must provide balanced, durable immunity against all four serotypes (DENV-1–4) to minimize ADE risk and improve vaccine safety and effectiveness.

9. REAL-WORLD EFFECTIVENESS:

- **Reduction in dengue disease:** Vaccination can reduce symptomatic dengue cases, particularly in populations with previous dengue exposure.
- **Protection against hospitalization:** Some dengue vaccines have demonstrated meaningful protection against **dengue-related hospitalization and severe disease**.
- **Serotype variation:** Effectiveness can differ among **DENV-1, DENV-2, DENV-3, and DENV-4**, making balanced protection important.
- **Previous infection matters:** A person's **baseline dengue serostatus** can influence vaccine effectiveness and safety.
- **Duration of protection:** Long-term follow-up is important to determine how well protection is maintained over time.
- **Population-level impact:** High vaccination coverage, combined with mosquito-control measures, can help reduce dengue transmission and healthcare burden.

10. KEY BENEFITS AND PUBLIC HEALTH IMPACT OF DENGUE VACCINATION

- The dengue vaccine plays a crucial role in diminishing symptomatic dengue infections, severe cases, hospitalizations, and the overall strain on healthcare systems.

- It has the potential to lessen outbreaks, avert complications, and safeguard at-risk populations in areas where the disease is prevalent.

- Extensive vaccination efforts bolster public health by curtailing transmission rates, decreasing treatment expenses, enhancing healthcare capabilities, and fortifying strategies for dengue prevention.

- When integrated with mosquito control measures and surveillance, vaccination aids in achieving a sustained decrease in dengue-related illnesses and fatalities**.**

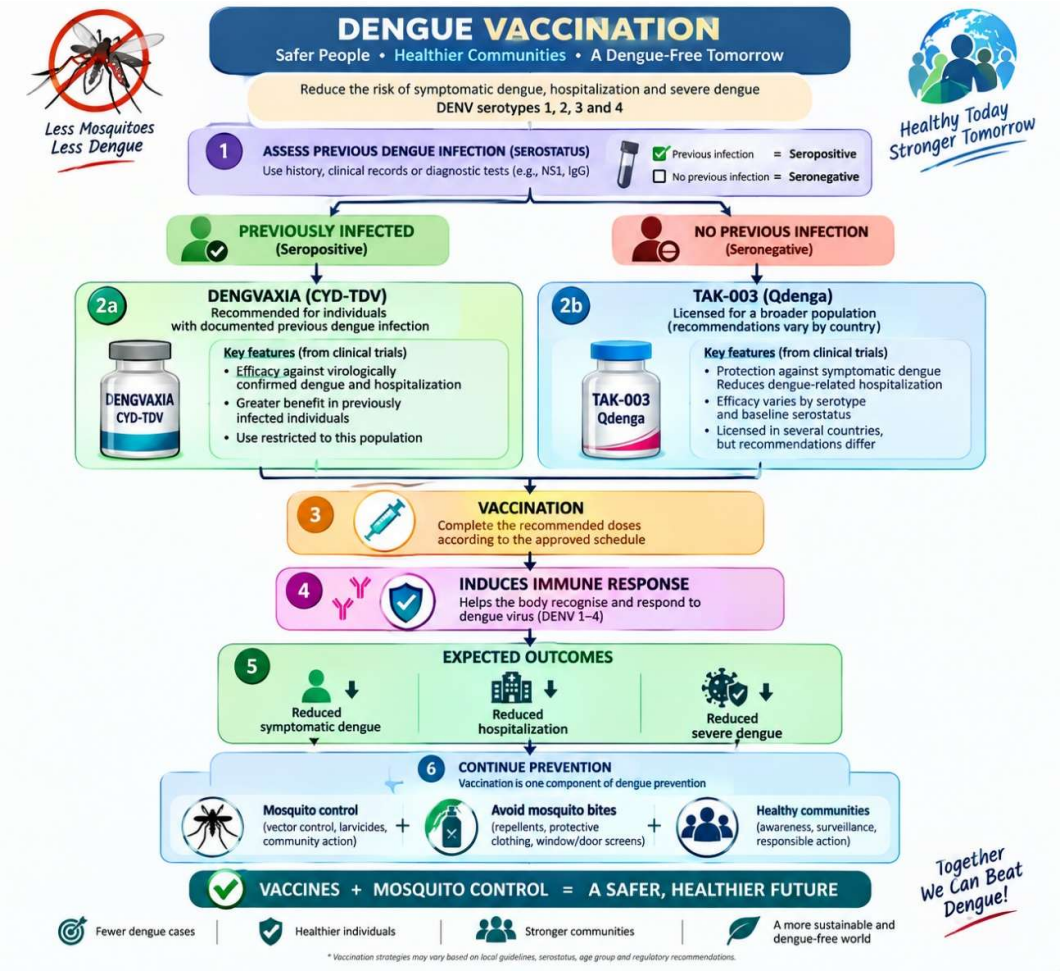


Figure:10- Dengue Vaccination Strategy: Evaluation, Selection of Vaccines, and Anticipated Results.

Table:5- The progression of dengue vaccine development has transitioned from traditional methods to innovative next-generation strategies.

Nanoparticle approach	**Antigen-loaded nanoparticles**	**Display or deliver antigens using nanoscale platforms**	**Enhanced antigen presentation and immune stimulation**	**Formulation and scalability**	**Multivalent nanoparticle vaccines**
Structural vaccinology	Structure-guided antigen design	Use molecular structures to identify and optimize protective epitopes	Rational and precise antigen engineering	Requires high-resolution structural and immunological data	Structure-guided tetravalent designs
Reverse vaccinology	Genome- and proteome-guided antigen discovery	Identify vaccine targets computationally	Enables systematic	Prediction requires	Integration with AI and multi-omics

			antigen screening	experimental validation	
AI-assisted design	Machine learning/deep learning	Predict epitopes, antigenicity, immunogenicity, and molecular interactions	Accelerates candidate discovery and optimization	Requires high-quality training data and experimental validation	Generative AI and integrated vaccine design
Systems immunology	Multi-omics immune profiling	Characterize complex vaccine-induced immune responses	Identifies biomarkers and mechanisms of protection	High-dimensional data analysis	Predictive and precision vaccinology
Next-generation design	Integrated computational + structural + immunological platforms	Combine AI, structural vaccinology, systems immunology, and advanced delivery	Potential for broader, safer, and longer-lasting protection	High development complexity and regulatory requirements	Broadly protective next-generation dengue vaccines

Dengue vaccines have demonstrated clinically meaningful preventive efficacy, but their performance is not uniform across all populations, serotypes, or baseline serostatus groups. Therefore, evaluation should consider not only overall vaccine efficacy but also **age, previous dengue infection, circulating serotypes, hospitalization, severe disease, duration of protection and safety**.

11. RESULT AND DISCUSSION

A notably promising avenue is the combination of structural vaccinology, AI-driven antigen design, systems immunology, and advanced delivery platforms. These multidisciplinary strategies could facilitate the identification of conserved protective epitopes, enhance antigen presentation, and forecast immune responses specific to different populations.

Recent progress in the development of dengue vaccines indicates a greater potential for achieving balanced immunity across all four DENV serotypes. Various platforms, including live-attenuated, recombinant, viral-vector, DNA, mRNA and VLP, have exhibited differing levels of immunogenicity and efficacy. The effectiveness of vaccines is affected by factors such as serostatus, age, viral genotype, and the intensity of transmission. Advancements in **structural vaccinology, epitope** for engineering, artificial intelligence could further enhance the safety, breadth, and durability of dengue protection.

12. CONCLUSION

The development of next-generation dengue vaccines necessitates a thoughtful approach to antigen design, ensuring balanced immunity across multiple serotypes, and enhancing safety for various populations. The incorporation of structural vaccinology, computational design, artificial intelligence, and systems immunology can expedite this process. Future strategies must focus on providing long-lasting protection, minimizing antibody-dependent enhancement, and ensuring effective implementation in diverse epidemiological contexts.

13. REVIEW FINDING:

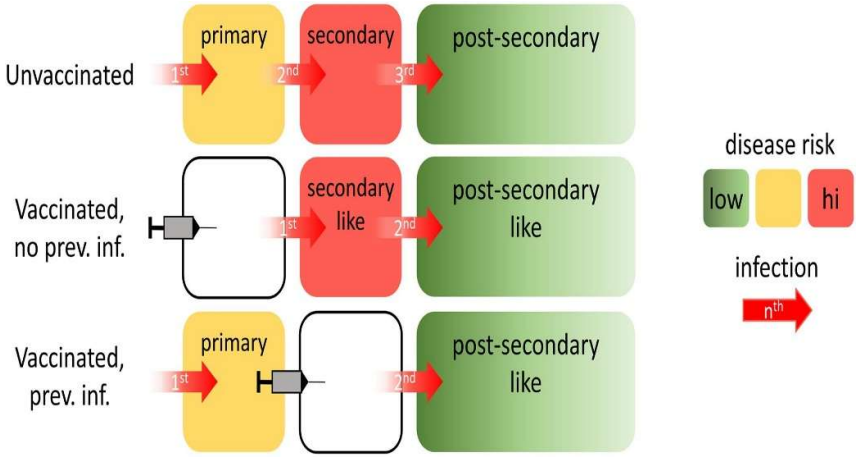


Figure:11-Impact of Vaccination and Previous Infection on Disease Risk.

This study examines the differences in disease risk and infection patterns between vaccinated and unvaccinated individuals. Unvaccinated individuals experience primary, secondary, and post-secondary stages of infection. In contrast, vaccination—regardless of prior infection—alters these stages and has the potential to lessen disease severity and overall risk in the event of future infections.

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