Vaccine as a control measure of Dengue: is it feasible?

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INTRODUCTION

Dengue is the most important arboviral disease worldwide, since 50% of the population in the world live in 125 countries where the disease is endemic (50-200 million infections/year, 20.000 deaths/year)[1]. This disease is caused by 4 serotypes of Dengue virus (DENV-1 to DENV-4) and it is transmitted to humans in tropical and subtropical countries by mosquito bites from the *Aedes* genus [2]. There are different kinds of clinical manifestations of the infection: asymptomatic disease, soft - nonspecific disease, classic feverish disease or severe disease (Dengue Haemorragic Fever – DHF – and Dengue Shock Syndrome – DSS -) [3].

The immune response is a key factor against the infection.

- Innate immunity: first barrier (INF production).
- Adaptive immunity: 6 days after the bite.

It brings either neutralization or enhancement of the infectivity of DENV:

- **Multiple hit phenomenon** (Neutralization).
- **Antibody-mediated enhancement of infection**, ADE (Enhancement).
- **Original antigenic sin** (Enhancement).
- **Massive production of cytokines and immunomodulators** (Enhancement).[2, 4]

VACCINES

Today, a Dengue vaccine is thought to be the most important preventive strategy in the future. The ideal vaccine should produce homotypic and heterotypic immune responses for all the serotypes. There are some challenges to achieve a good vaccine, being the ADE phenomenon the most important to overcome [4, 5, 6].

Live Attenuated Vaccine[2, 5, 6]

- DENV is attenuated through serial tissue culture passages. It induces adaptative immune responses against structural and non-structural proteins of the virus → Most similar to induced natural immunity.

- **Walter Reed Army Research Institute** (WRAIR) → Phase II.
- **Mahidol University** (Bangkok).

Chimeric Virus Vaccine [2, 5, 6, 8]

-Specific protein encoding genes substitution of one virus for those of another.

- **ChimeriVax Dengue Tetravalent Vaccine (CVD1-4)** → DENV wt - Yellow Fever Virus 17D chimera (prM and E proteins). Phase II.
- **DENVax** → DENV-2 backbone – prM and E proteins DENV-1, 3, 4 chimera. Phase I.

Virus Subunit Vaccine [5, 10, 11]

- Structural proteins or domains produced in expression systems → Domain III of E protein (EDIII).

- **r80E** → Truncated recombinant protein (20% protein removal at C-terminal). Phase I.
- **LcEDIII** → Lipidated EDIII consensus (DENV-1 to DENV-4), without adjuvants.
- **DIIIC-2** → DENV-2 EDIII – C protein fusion , with adjuvants.
- **Tet-EDIII – Co1 constructions** → Oral vaccine project.

Virus – Vectored Vaccine [5, 6]

- Use of different viruses as expression vectors of DENV genes, resulting in the expression of its antigenic proteins → Virus Replicon Particles (VRP).

- **cAdVax-DenTV** → Adenovirus (vector) – DENV prM/E proteins construction. Pre-clinical phase.

Targeted Mutagenesis Live Atenuated Vaccine [2, 5, 6, 7]

-Targeted mutagenesis to attenuate DENV → Δ30 dNTPs in 3'-UTR of cDNA. Clones of DENV-4 and DENV-1 showed optimal immunogenicity; DENV-2 and DENV-3 non-functional (under-attenuation).

- Use of **DENV-4Δ30** as a **genetic backbone** for serotypes 2 and 3.
- **Mutation** in **E protein** (E-$Glu_{345}K$) of DENV-4/ DENV-4Δ30.

Inactivated Virus Vaccine [5, 9]

-Multiple Vero cells culture passages of DENV and formalin inactivation once they are purified.

- **TDENV PIV** → Phase I (WRAIR).

DNA Vaccine [5, 6]

-Encoding antigenic genes cloned into a plasmid vector, inducing a protective cytotoxic immune response.

- Low efficiency: difficulty for exogenous DNA to enter the host cells.

- **WRAIR** → prM and E encoding genes. With adjuvants.
- **NS1 an encoding gene** → NS1 induces specific serotype immune responses.

Virus Like Particles Vaccine [12]

- Spherical membrane vesicles containing prM/E proteins embedded in a lipid bilayer, with or without a nucleocapsid → Virion imitation.

- There are still factors to be understood (*in vivo* and *in vitro* different results).

CONCLUSIONS

Dengue is a worldwide health problem and vaccination is considered as the future ideal strategy to solve it. There are still some factors of the disease to be understood in order to find an efficient vaccine that does not enhance the disease or cause critical side effects. However, the positive results obtained in research are making feasible the Dengue vaccine as the solution to reduce the burden of the disease in the future.

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