MEDICAL ACADEMY NAMED AFTER S.I. GEORGIEVSKY

DEPARTMENT OF MICROBIOLOGY

DENGUE VACCINES AND CHALLENGES IN DENGUE VACCINE DEVELOPMENT

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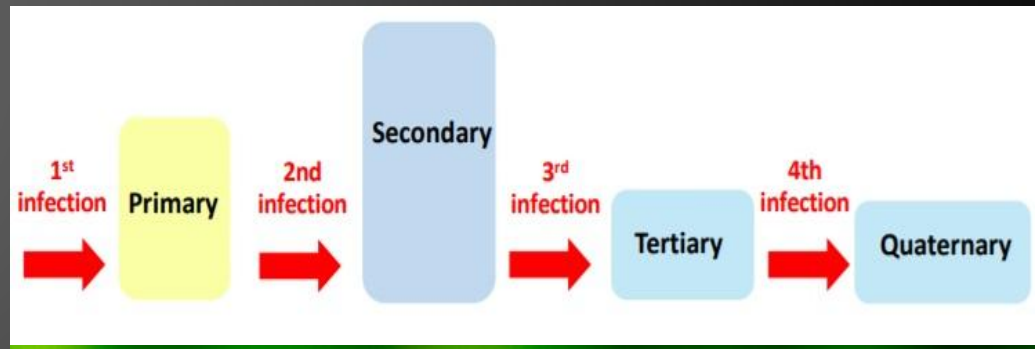
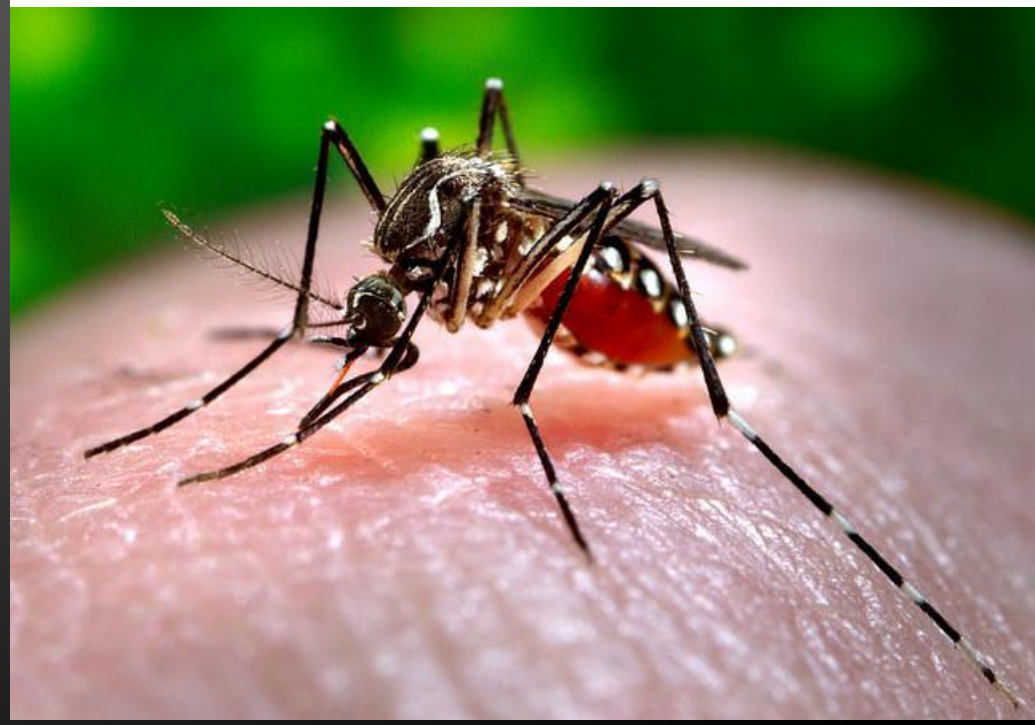
Overview of Dengue

- DENGUE OR "BREAKBONE FEVER" IS A RAPIDLY EXPANDING ARBOVIRAL DISEASE TRANSMITTED BY AEDES MOSQUITOES.
- FOUR ANTIGENICALLY DISTINCT SEROTYPES (DENV1-4).
- CLINICAL SPECTRUM:
  - 100-400 MILLION INFECTIONS PER YEAR GLOBALLY.
  - 80% ASYMPTOMATIC
  - SELF-LIMITING FEBRILE ILLNESS
  - SEVERE DENGUE (~2-4% OF SYMPTOMATIC)
  - CFR (CASE FATALITY RATE) 0.1—1%
  - SECONDARY INFECTIONS ARE ASSOCIATED WITH HIGHER RISK OF MORE SEVERE DENGUE





NECESSITY OF DENGUE VACCINE?

- Developing a dengue vaccine is a global health priority.
- Lack of specific Antiviral medication.
- Treatment is supportive and symptomatic such as:
  - Replacement of Plasma losses.
  - Correction of Electrolyte and metabolic disturbances
  - Platelet Transfusion if needed.
    (When Platelet Count is 10,000 or less)

Dengue Vaccine development

World Health Organization

(http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/)

DPIV
GlaxoSmithKline, Biomanguinhos, WRAIR

DEN-80E
Merck

TVDV
Naval Medical Research Center

TLAV-TPIV
WRAIR

TV003/TV005
US National Institutes of Health[1]
Butantan

DENVax
Takeda

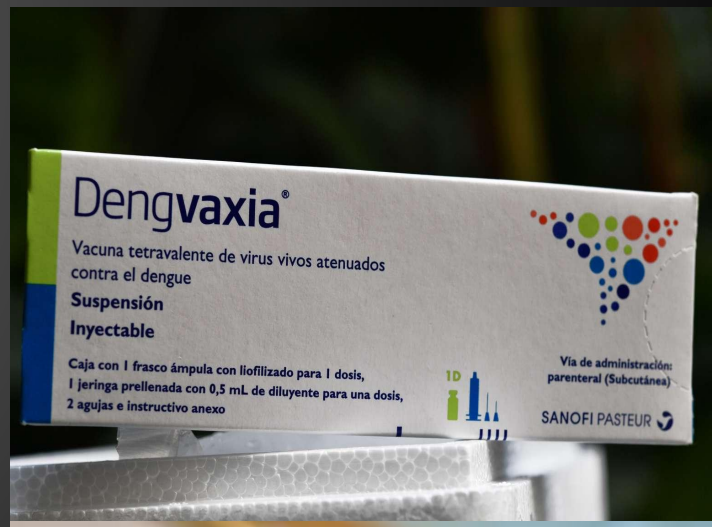
CYD-TDV
Dengvaxia™
Sanofi Pasteur

CYD-TDV
SANOFI PASTEUR

- Several vaccine candidates are under phases of development, including live attenuated virus vaccines, live chimeric virus vaccines, inactivated virus vaccines, subunit vaccines, DNA vaccines and viral-vectored vaccines.

DENGVAXIA (CYD-TDV):

- THIS VACCINE HAS BEEN LICENSED FOR HUMAN USE SINCE 2015.
- IT IS A CHIMERIC YELLOW FEVER-DENGUE, LIVE-ATTENUATED, TETRAVALENT DENGUE VACCINE (CYD-TDV); DEVELOPED BY SANOFI PASTEUR.
- IT USES LIVE ATTENUATED YELLOW FEVER 17D VIRUS AS VACCINE VECTOR IN WHICH THE TARGET GENES OF ALL FOUR DENGUE SEROTYPES ARE INTEGRATED BY RECOMBINANT TECHNIQUE
- AGE: IT IS INDICATED FOR 9-45 YEARS OF AGE
- SCHEDULE: 3 INJECTIONS OF 0.5 ML ADMINISTERED SUBCUTANEOUSLY AT 6 MONTH INTERVALS
- IT IS AVAILABLE AS LYOPHILIZED FORM; RECONSTITUTED WITH NORMAL SALINE
- CONTRAINDICATIONS: (I) ALLERGIC REACTIONS TO VACCINE; (II) IMMUNODEFICIENT INDIVIDUALS (E.G. HIV) (III) PREGNANT AND BREASTFEEDING WOMEN
- EFFICACY AGAINST HOSPITALIZED DENGUE ILLNESS WAS FOUND AROUND 80%
- WHO RECOMMENDS THIS VACCINE TO START IN HIGH BURDEN COUNTRIES (SEROPREVALENCE > 70%)
- WHO ALSO RECOMMENDS DENGVAXIA BE USED ONLY IN PEOPLE PREVIOUSLY INFECTED WITH DENGUE. FOR SERONEGATIVE PEOPLE THERE MAYBE HIGHER RISK OF DEVELOPING SEVERE DENGUE.
- CURRENTLY, THE VACCINE IS APPROVED IN MEXICO, PHILIPPINES, BRAZIL, INDONESIA, THAILAND AND SINGAPORE.



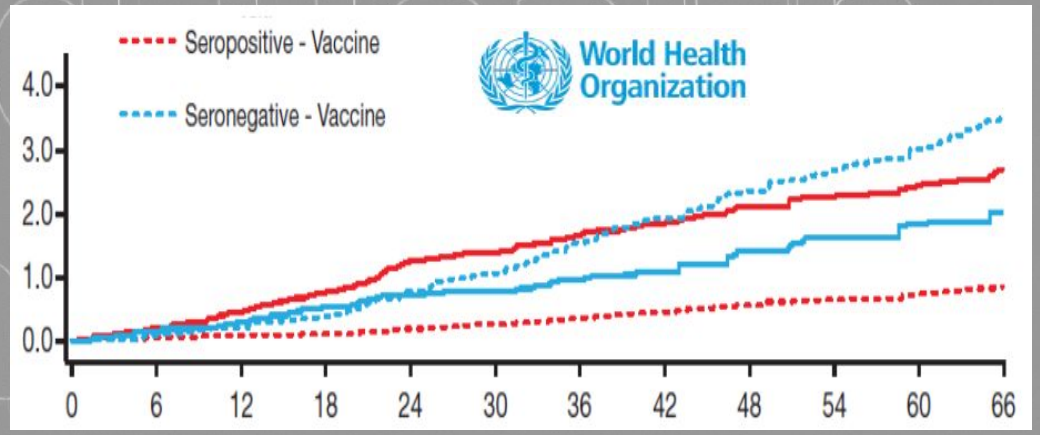
STRATEGY FOR VACCINATION:

- **POLICY OPTIONS OF WHO:**

1. SCREEN AND VACCINATE – SCREEN EVERY POTENTIAL VACCINE RECIPIENT WITH A RAPID DIAGNOSTIC TEST (RDT) TO DETERMINE SEROSTATUS, AND ONLY VACCINATE THOSE TESTING SEROPOSITIVE.

2. MASS-VACCINATION WITH SEROPREVALENCE THRESHOLD – VACCINATE POPULATIONS IN AREAS WHERE TRANSMISSION INTENSITY EXCEEDS A CERTAIN THRESHOLD – E.G. >80% SEROPREVALENCE IN 9 YEAR OLD CHILDREN.

Cumulative risk of hospitalized dengue



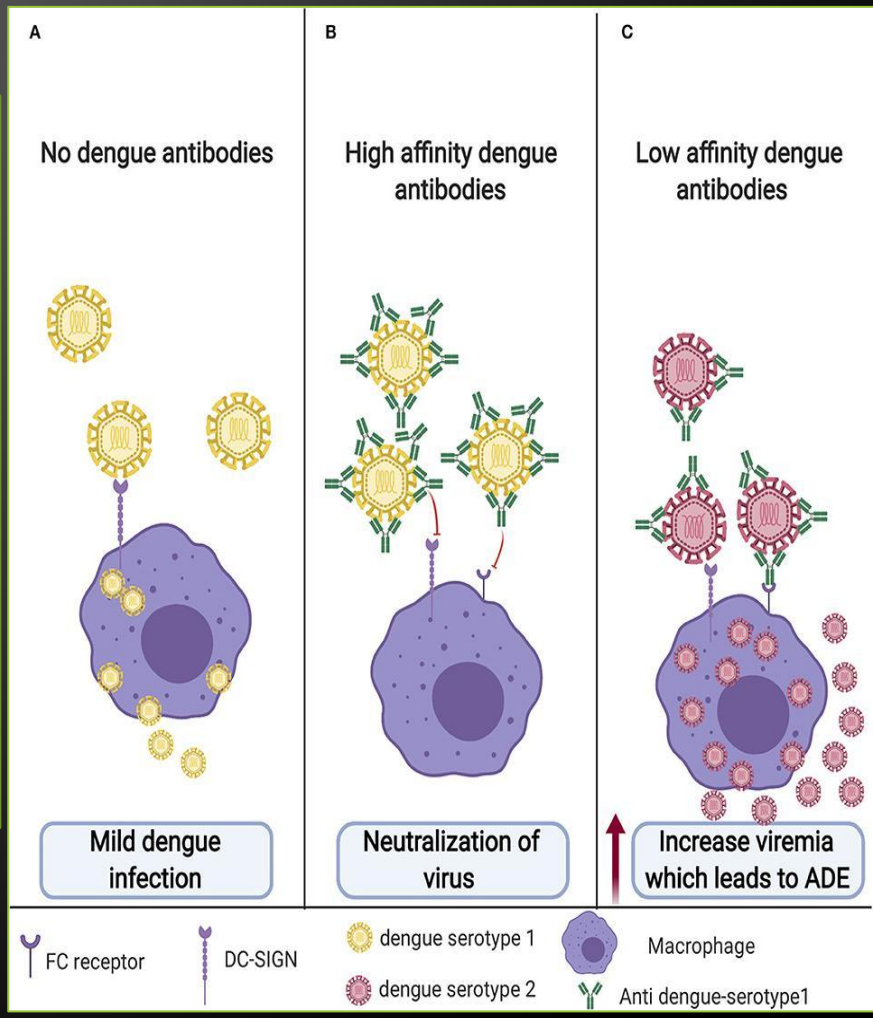
- **WHO POSITION: PRE-VACCINATION SCREENING:**

1. **SCREENING TESTS WOULD NEED TO BE HIGHLY SPECIFIC TO AVOID VACCINATING TRULY SERONEGATIVE PERSONS.**
2. **NO SCREENING TEST IS LIKELY TO BE 100% SPECIFIC DUE TO POTENTIAL CROSS-REACTIVITY WITH OTHER FLAVIVIRUSES.**

ANTIBODY RESPONSE AGAINST DENV

- Infection with DENV induces production of NEUTRALISING and NON-NEUTRALISING Antibodies

NEUTRALISING	NON-NEUTRALISING
• PROTECTIVE IN NATURE • PRODUCED BOTH AGAINST INFECTIVE AND OTHER SEROTYPES • FOR INFECTIVE SEROTYPES ANTIBODIES LAST LIFELONG • FOR OTHER SEROTYPES IT DIMINISHES OVER FEW MONTHS	• HETEROTYPIC IN NATURE; I.E. THEY ARE PRODUCED AGAINST OTHER SEROTYPES BUT NOT AGAINST THE INFECTIVE SEROTYPES. • LASTS LIFELONG. • SHOW ADE (ANTIBODY DEPENDENT ENHANCEMENT) PHENOMENON.



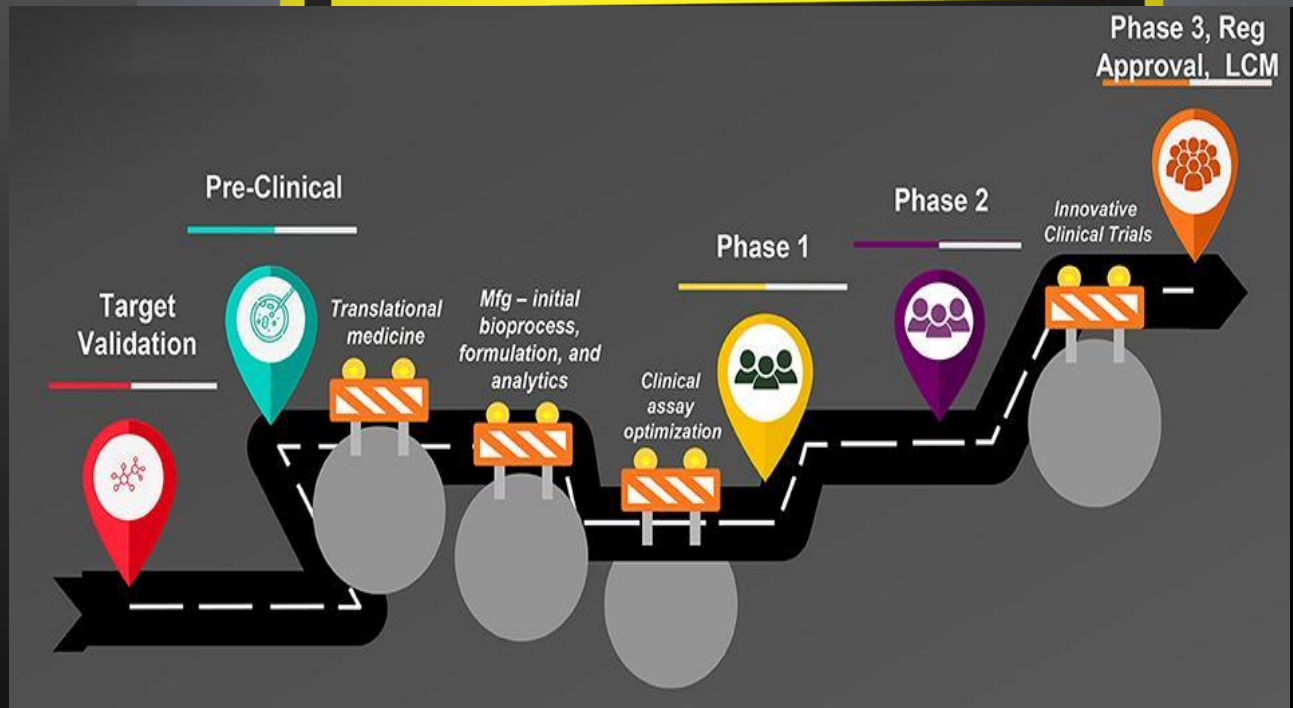
DENGUE VACCINE

IS NOT FOR EVERYONE !!!

ADE- NON-NEUTRALISING ANTIBODY PRODUCED FOLLOWING THE FIRST SEROTYPE INFECTION, CAN BIND TO A SECOND SEROTYPE DURING SECONDARY DENGUE INFECTION; BUT INSTEAD OF NEUTRALISING THE SECOND SEROTYPE IT PROTECTS IT FROM HOST IMMUNE SYSTEM BY INHIBITING THE BYSTANDER B-CELL ACTIVATION AGAINST THE SECOND SEROTYPE.

Difficulties in Developing DENV Vaccine:

- VACCINE DEVELOPMENT FOR DENGUE HAS BEEN A CHALLENGE AT IT SHOULD BE EFFECTIVE AGAINST ALL FOUR SEROTYPES AND ELICIT EQUAL AND LONG-LASTING IMMUNITY TO ALL FOUR SEROTYPES SIMULTANEOUSLY.
- ADDITIONALLY, THE ADAPTIVE IMMUNE RESPONSE TO DENV MAY BE BOTH PROTECTIVE AND PATHOGENIC UPON SUBSEQUENT INFECTION, AND THE PRECISE FEATURES OF PROTECTIVE VERSUS PATHOGENIC IMMUNE RESPONSES TO DENV ARE UNKNOWN, COMPLICATING VACCINE DEVELOPMENT.



CONTD..

- VACCINE DEVELOPMENT IS CONSIDERED CHALLENGING DUE TO THE SEVERITY OF THE DISEASE OBSERVED IN INDIVIDUALS WHO HAVE ACQUIRED DENGUE-SPECIFIC IMMUNITY, EITHER PASSIVELY OR ACTIVELY.
- THERE'S NO ANIMAL MODEL FOR DENGUE PRESENTLY AVAILABLE (WHICH MAKES EARLY TRIALS DIFFICULT TO CONDUCT OR DESIGN) AND ABSENCE OF SUITABLE MARKERS OF PROTECTIVE IMMUNITY.

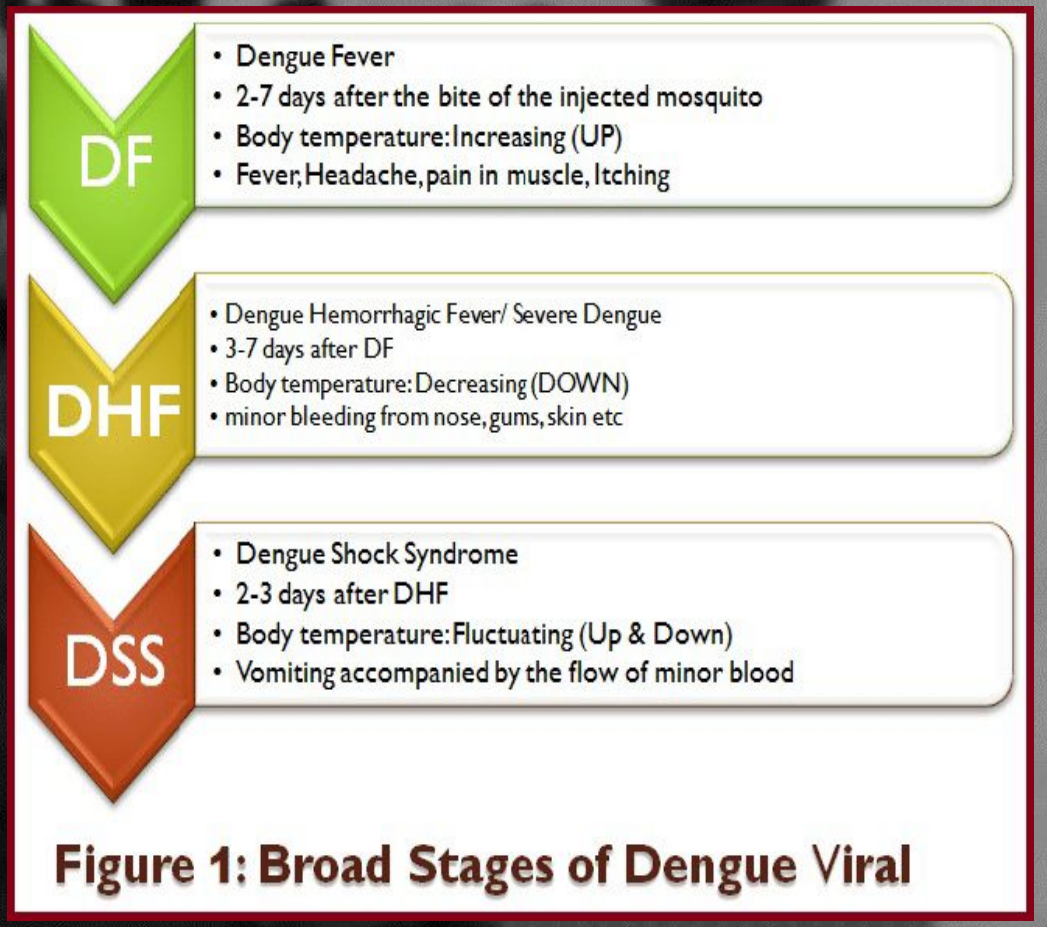
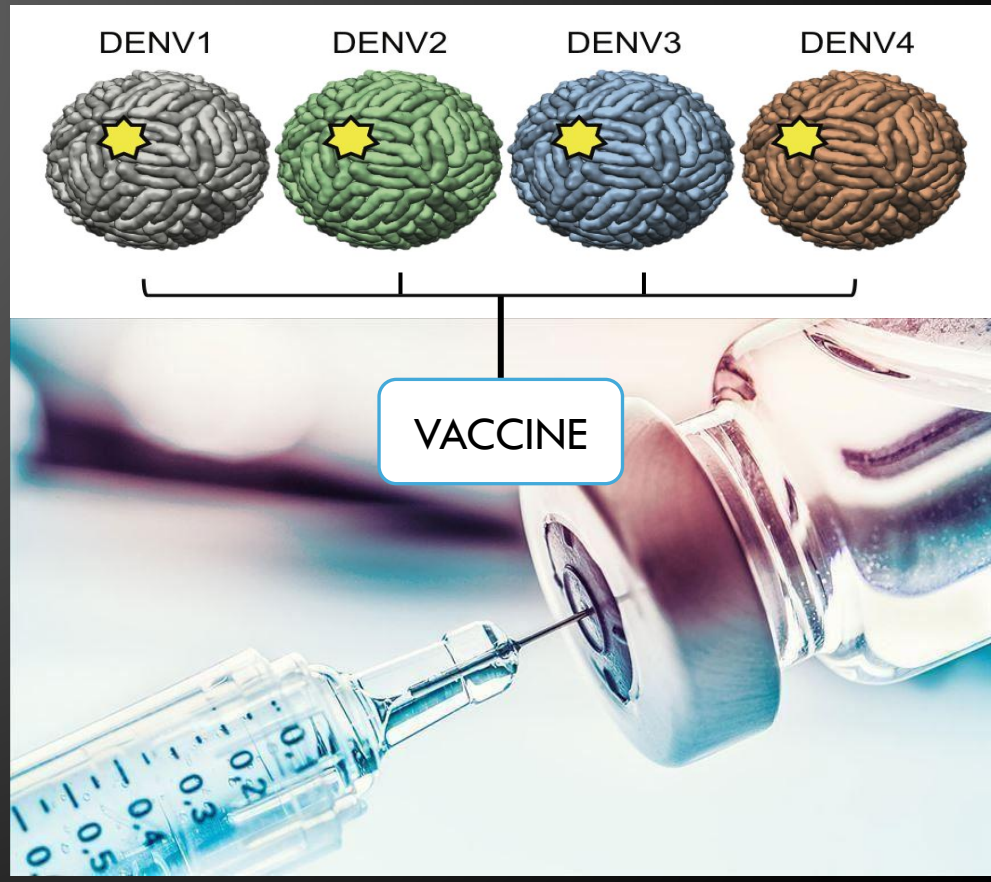


Figure 1: Broad Stages of Dengue Viral

CONCLUSION:

- FIND A VACCINE AGAINST ONE VIRUS COULD TAKE MANY YEARS.
- AND FINDING VACCINE AGAINST FOUR VIRUSES, TRYING TO HAVE THOSE FOUR INDIVIDUAL VACCINES TO BE PUT TOGETHER IN ONE VACCINE, AND STILL WORK AS WELL.
- THIS MAKES THE VACCINE DEVELOPMENT PROCESS DIFFICULT AND CUMBERSOME.

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