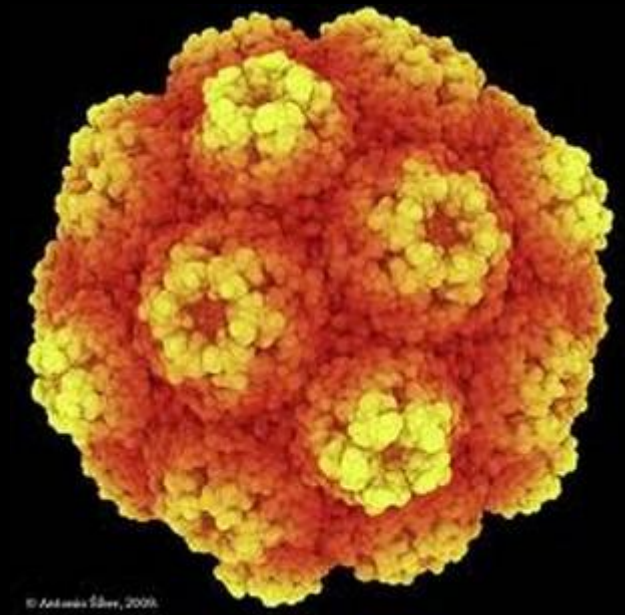
YELLOW FEVER VACCINE – PAST, PRESENT & FUTURE

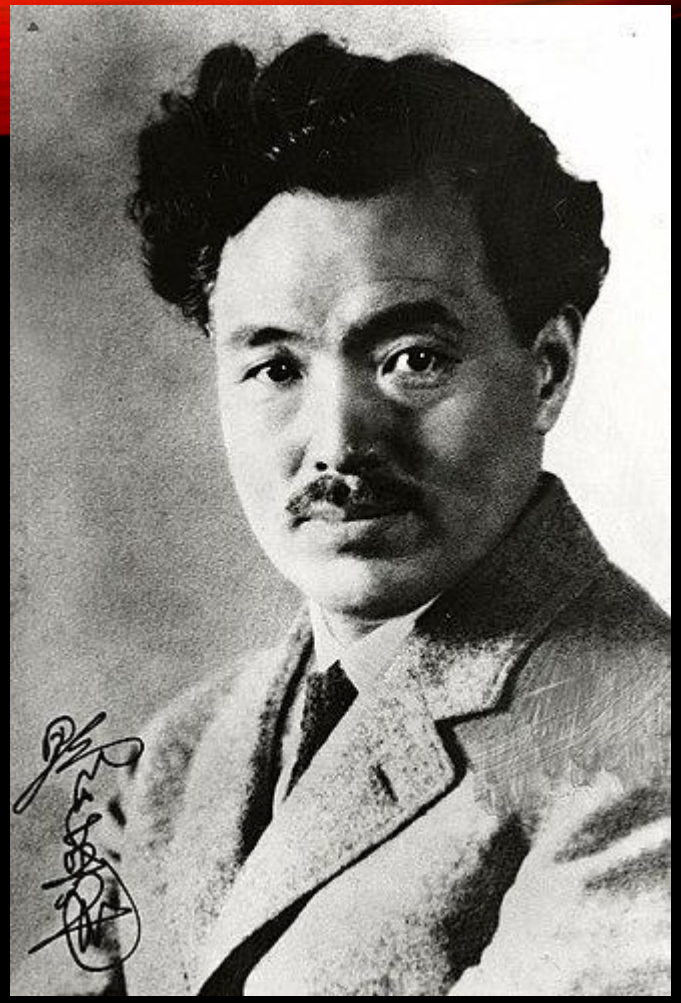
YELLOW FEVER VIRUS

- Arbovirus
- Family – Flaviviridae
- Genus – Flavivirus
- Single serotype
- Reservoir - Monkeys
- Vector – Aedes Aegypti
- Endemic to Africa & South America
- No specific anti-viral treatment
- Vaccination

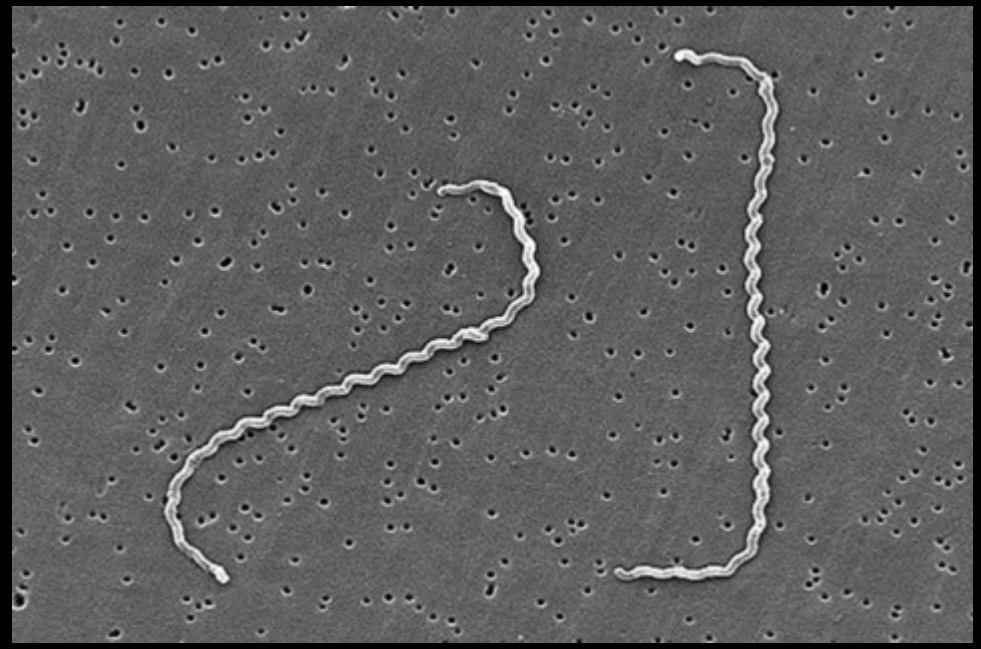


PAST

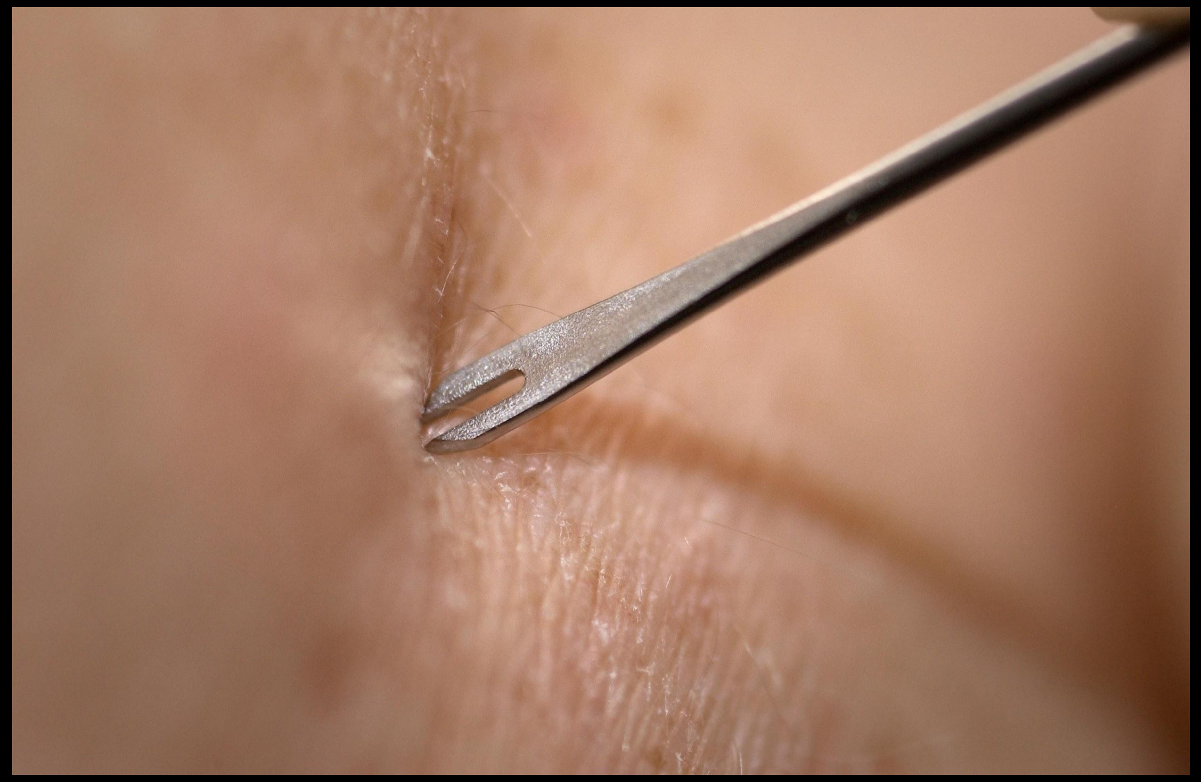
- 1912 – opening of Panama canal – increased global exposure – first modern attempt for vaccine development



- Hideyo Noguchi, a Japanese bacteriologist – worked for Rockefeller Foundation, Ecuador – Vaccine based on disease caused by leptospiral bacterium.



- Resulting vaccine – ineffective – eventually abandoned.

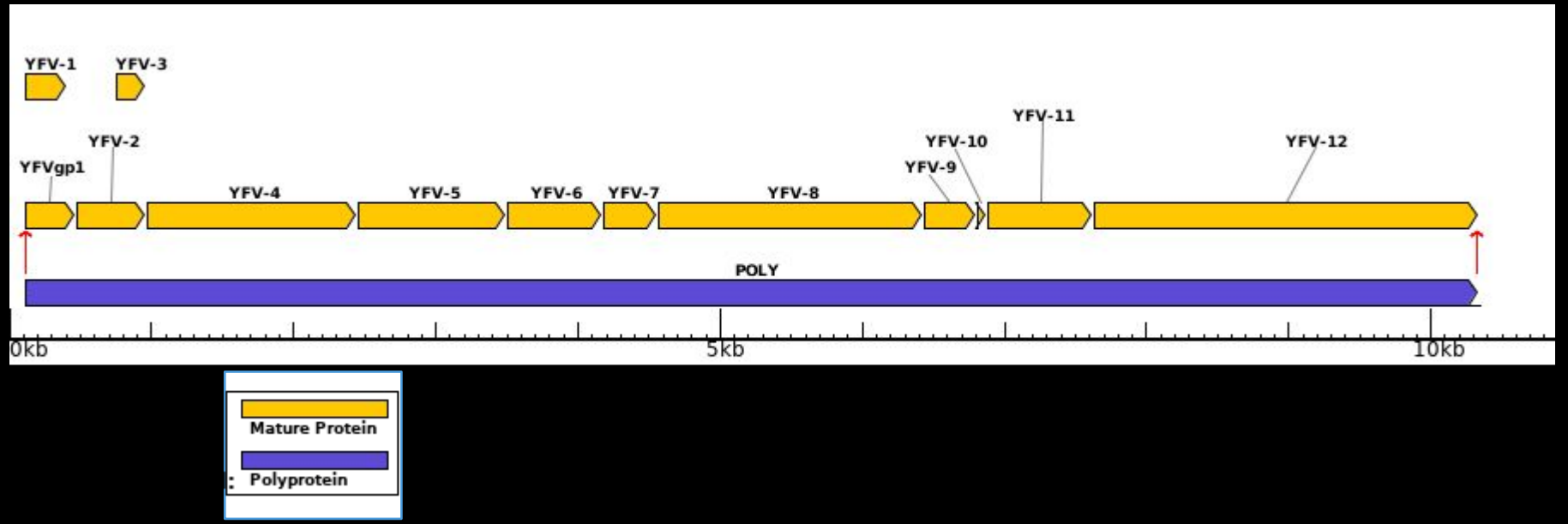


- "French strain" – obtained from a survivor – another vaccine by Pasteur Institute scientists.
- Administered by scarification, like smallpox vaccine – given in combination – immunity to both diseases.
- But severe systemic and neurologic complications were observed.

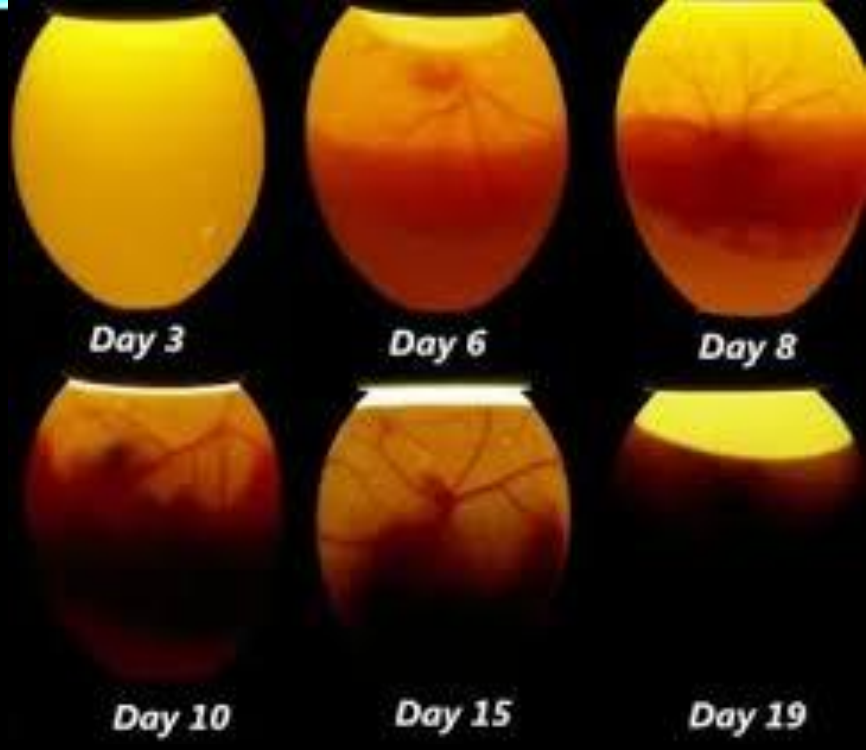
- Attempts to attenuate – failed.

- Another vaccine developed – derived from Asibi in 1927.
- First isolation from human.
- Safer
- Limited widespread use – due to use of large amount of human serum.

- In 1937, Max Theiler (awarded the Nobel Prize in Physiology or Medicine in 1951 for developing a vaccine against yellow fever) with Hugh Smith & Eugen Haagen at the Rockefeller Foundation to improve the vaccine from the "Asibi" strain, discovered that a favorable chance mutation in the attenuated virus had produced a highly effective strain that was named 17D.



- Theiler used chicken eggs to culture the virus.
- Over 1 million people vaccinated by 1939 – after brazil field trials.



Widely used by U.S. Army during WW-II.

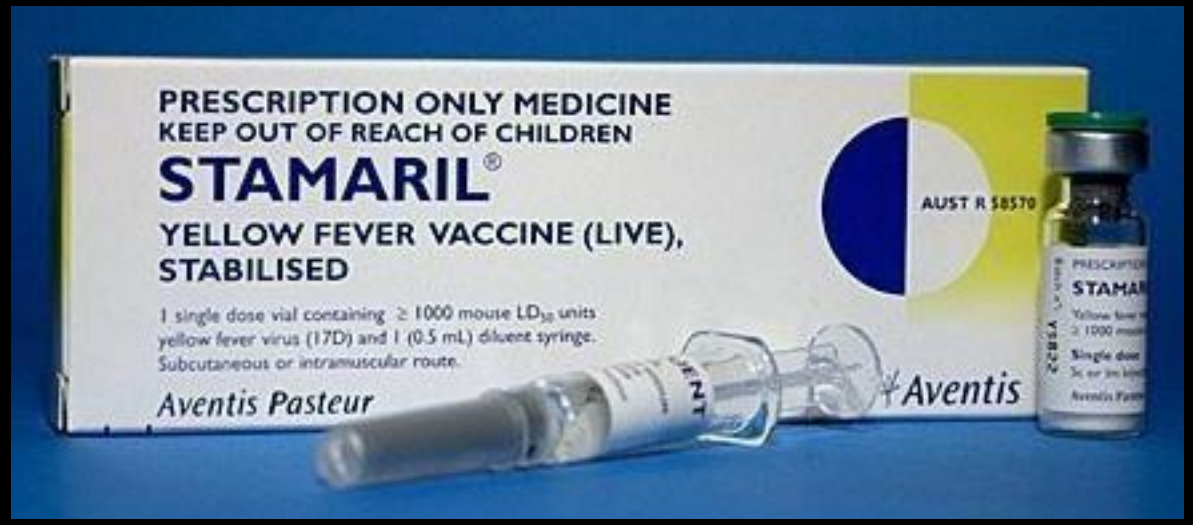
- Theiler's vaccine – largest outbreak of Hepatits B – 330,000

- In 1941 – "aqueous-base" version of 17D vaccine – distilled water combined with virus grown in chicken eggs.

PRESENT

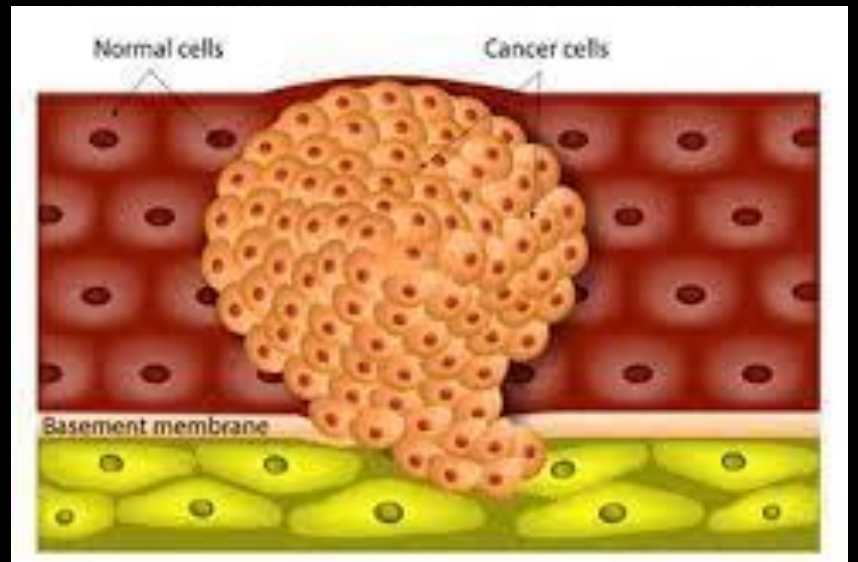
- Currently available YF-vaccines (WHO prequalified)

1. Bio-manguinhos, 17-DD, Brazil
2. Sanofi Pasteur, Stamaril, 17D-204, France
3. Pasteur Institute Dakar, 17D-204, Senegal
4. Chumakov Institute, 17D-204, Russian federation
5. Sanofi Pasteur, YF-Vax, 17D-204, USA



- **Contraindiction**

1. Allergy to vaccine component (Egg protein)
2. Age < 6 months
3. Symptomatic HIV infection/CD4+ counts < 200 per mm^3
4. Thymus disorder
5. Primary immunodeficiencies
6. Malignant neoplasms
7. Transplantation
8. Immunosupressive and immunomodulatiory therapies



- **Precaution**

1. Age 6-8 months
2. Age ≤ 60 yrs
3. Asymptomatic HIV & CD4+ counts 200-499 per mm^3
4. Pregnancy
5. Breast feeding

- Common adverse events of YF Vaccines

1. Fever, headache, backache 3-7 days after vaccination: 5-15%
2. Injection site inflammation 1-5 days after vaccination: 1-30%

- WHO YF vaccines recommendations:

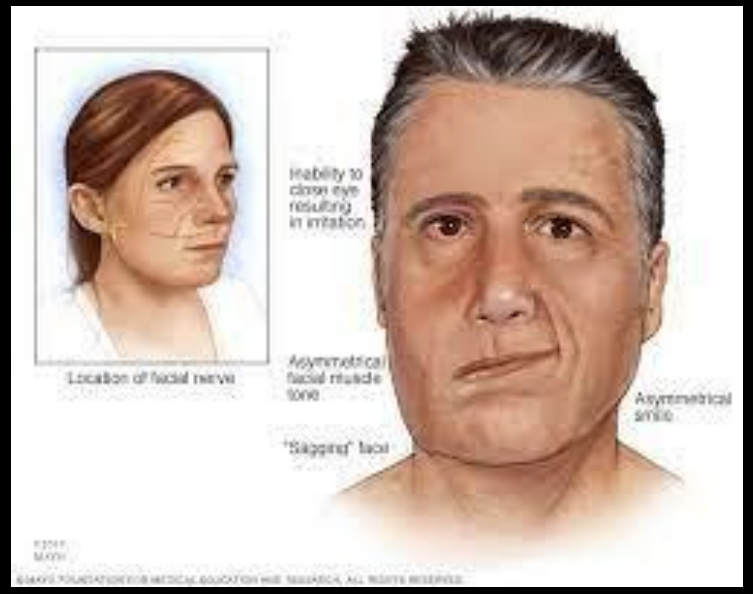
- SAGE formed YF Vaccine workgroup in 2011: Need for booster dose every 10 years to maintain protection against yellow fever
- Safety of YF Vaccine in selected special populations
- Co-administration of YF and other vaccines
- Single subcutaneous dose IHRs require revaccination at intervals at 10 yrs to boost antibody titers

YF VACCINE ASSOCIATED DISEASE

1. Neurogenic- due to direct viral invasion of CNS or auto-immune mediated, can lead to most common meningoencephalitis

   Others – GBS, ADEM, Bulbar palsy, Bell's palsy

   Onset median- 11 days post vaccination



2. Viscerotrophic disease

   Severe illness similar to wild-type disease

   Onset median – 3 days post vaccination

   Tend to affect younger females and older males

   63% fatality rate

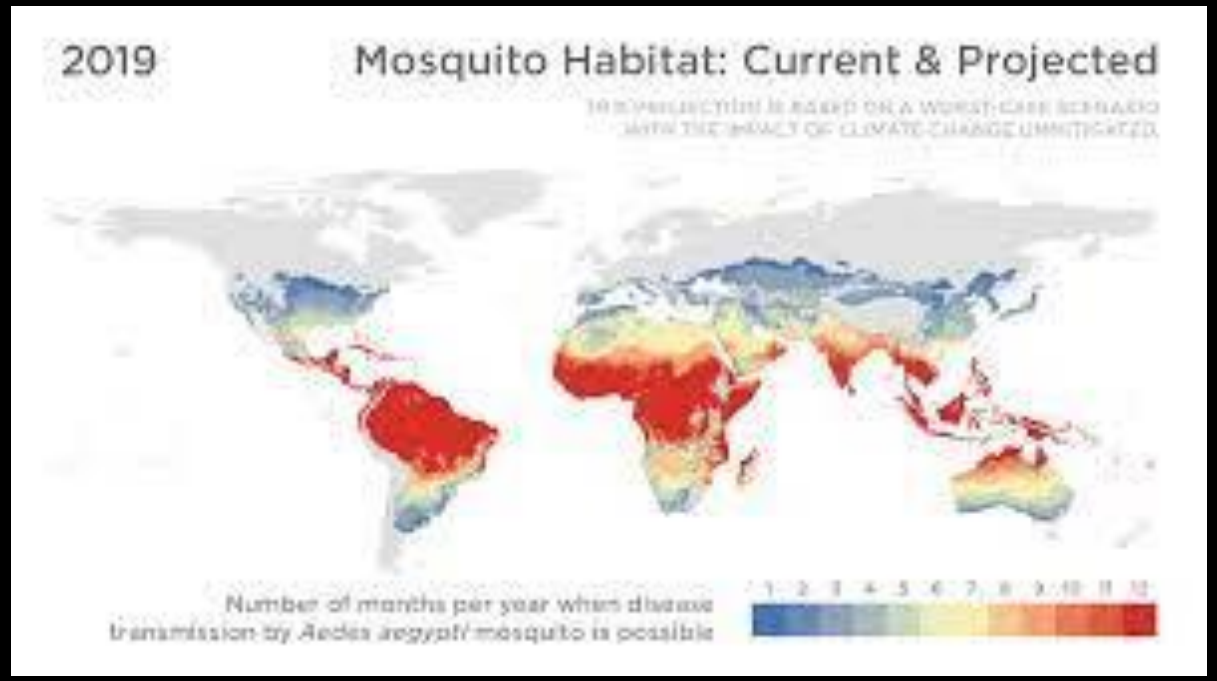
WHO EYE INITIATIVE

- "Eliminate Yellow Fever Epidemics"
- Aims to increase 17D vaccine manufacturing to distribute 1.3 billion vaccine doses to endemic countries by 2026.

FUTURE

- Present issues to be solved to prevent future epidemics:

1. Finite vaccine seed-lot system
2. Limited vaccine manufacturing capabilities using embryonated chicken eggs
3. Climate change pushing mosquito habitats to new regions
4. Recent epidemics exposing issues in rapid vaccine dissemination
5. Storage problems



- Solutions

1. A more shelf-stable vaccine - more doses generated with fewer IU per dose

- YF-Vaccines in development and their benefits:

1. inactivated vaccines - allow those over 60 to receive a primary dose of vaccine (Eg. XRX-001 vaccine highly immunogenic with antibody titers similar to live-17D vaccine)
2. recombinant vaccine constructs - higher immunogenicity with lower dose and least side-effects (Eg. 105 TCID50)
3. plasmid-vectored DNA constructs – quick production of neutralizing antibodies
4. virus-like particles (VLPs) – replication incompetent
5. mRNA vaccines – fast manufacturing
6. Synonymous mutations in live-attenuated vaccines - Deoptimizing multiple codons can attenuate viruses, as well as lower the risk of reversion and recombination of the attenuated virus
7. Plant-produced subunit vaccines – reduce dependence on chicken embryo culture, using Nicotiana benthamiana (in progress)

THANK YOU FOR ATTENTION.