Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases

Vaccines for arboviruses

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CDC disclaimer

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of [the Centers for Disease Control and Prevention

Outline

- Chikungunya vaccines
- Japanese encephalitis vaccines
- Zika vaccines
- West Nile vaccines
- Dengue vaccines

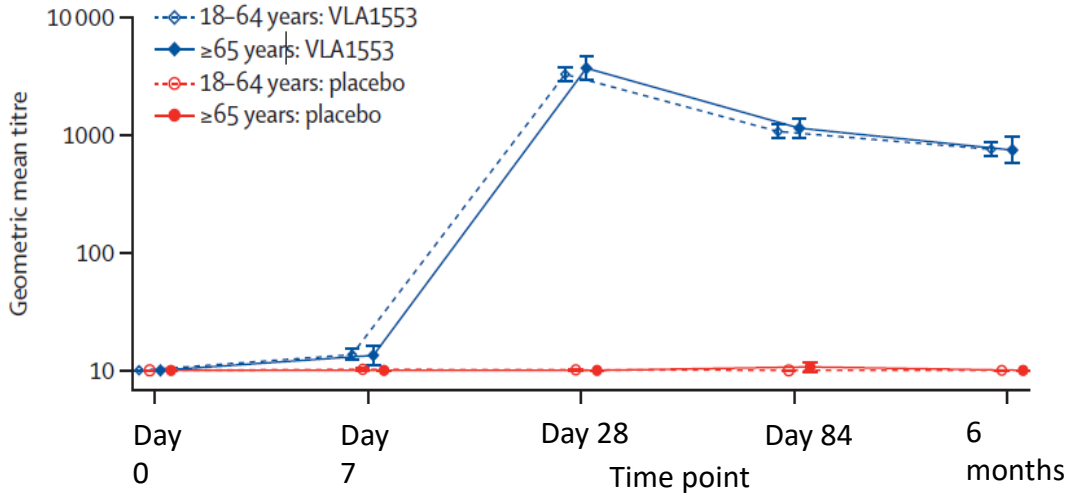
Chikungunya virus

PAHO Chikungunya Photo Story

Live attenuated chikungunya vaccine (VLA1553, Valneva)

- Licensed by FDA for adults aged ≥18 years under accelerated approval
- US Advisory Committee on Immunization Practices (ACIP) rec for travelers and lab workers Feb 2024
- Under review at European Medicines Agency (EMA)
- WHO at initial stages
- Coalition for epidemic preparedness innovations (CEPI) funding to ensure accelerated access to low/middle income countries

Geometric mean titer by time after intervention and age group



Adapted from Schneider et al., 2023
Vaccine n=266 placebo n=96

97% maintain antibody titers at 24m

Courtesy of Susan Hills CDC

Other chikungunya vaccines

- Virus-like particle vaccine, single dose
  - Manufactured by Bavarian Nordic
  - Phase 3 studies completed (adolescents, adults)
  - License applications to US FDA and European Medicines Agency planned for 2024

- Inactivated whole virus vaccine (BBV87)
  - Collaboration between International Vaccine Institute, Korea and Bharat Biotech, India
  - 2-dose primary schedule
  - Phase 2/3

Courtesy of Susan Hills CDC

Challenges chikungunya vaccines

- No efficacy data from phase 3 trials
- No clear correlate of protection
- Accelerated approval pathway has implications for post-licensure studies
- Long term protection unknown
  - 1 year follow up with Valneva and 6 months for Bavarian
- Vaccine supply, although CEPI support helps with access
- Ideal implementation strategy unknown
  - Routine immunization of adults in risk areas, outbreak response?

Japanese encephalitis virus

https://www.outlookindia.com/website/story/india-news-japanese-encephalitis

Japanese encephalitis virus (JEV) vaccines

- Vaccines have been available for decades
- Most endemic countries have vaccination programs
- Human cases occur in rural areas where people live and work close to pigs
- GAVI has expanded use of WHO-prequalified JEV vaccines
- SA 14-14-2 (CD-JEV) live attenuated vaccine was developed in China
  - Available at low cost to low and middle-income countries
- Several inactivated Vero cell culture-based and live attenuated vaccines easier to manufacture
- Ixiaro is the only licensed and available vaccine in the US

Vanice KS, et al. The future of Japanese encephalitis vaccination. Vaccines 2021, 6:82.

Challenges JEV vaccine

- Predicting transmission
- Vaccine production
- Global supply

Vanice KS, et al. The future of Japanese encephalitis vaccination. Vaccines 2021, 6:82.

Zika virus

https://www.paho.org/en/topics/zika

Zika vaccines

- Multiple Zika virus vaccine candidates in clinical trials including purified inactivated, live attenuated, viral vectored, recombinant subunit, DNA, mRNA vaccines
- Evaluated first in animal models (mice and non-human primates)
- Congenital Zika syndrome may develop from infection at any point during pregnancy so a ZIKV vaccine must induce protection against infection

Wang Y et al. Current advances in Zika vaccine development. Vaccines 2022, 10, 1816.

Challenges Zika vaccines

- Cases have declined making phase 3 trials to assess efficacy unfeasible
- Absence of validated immune correlate of protection
- Small number of participants does not allow ruling out increased risk of severe outcomes such as GBS
- Ethical issues in conducting efficacy trials in pregnant women
- Vaccine mediated antibody dependent enhancement (ADE) for dengue
- Efficacy may vary based on dengue exposure
- Alternative licensing pathways are needed
  - Efficacy from human challenge models
  - Extrapolation of protection to humans from adequate animal challenge models

West Nile virus

https://www.cdc.gov/westnile/index.html

West Nile virus (WNV) vaccines

- Several veterinary vaccines have been licensed
- No human WNV vaccines have been authorized
- Human studies have been conducted (two live attenuated chimeric, one DNA, one recombinant subunit, and two inactivated whole-virus vaccines), none progressed beyond phase 1 or 2
- All were associated with minimal adverse events, and most were shown to have favorable immunogenicity
- ChimeriVax-WN02 (YF17D backbone) only one studied in phase II and closest to licensure

Gould CV et al. Combating West Nile Virus Disease- time to revisit vaccination. NEJM 2023, 388, 1633-36.

Challenges WNV vaccines

- Sporadic and unpredictable nature of WNV makes efficacy trials challenging
- Severe disease in a subset of the population (>50 years and comorbidities)
- Trial endpoints? preventing neuroinvasive disease, all disease or infection affects feasibility
- Concerns with adverse events from live attenuated vaccines in the group at highest risk
- Cost and cost-effectiveness of WNV vaccine programs
- Alternative licensing pathways are needed
  - Immune protection in animal models of disease
  - Immunological markers

Gould CV et al. Combating West Nile Virus Disease- time to revisit vaccination. NEJM 2023, 388, 1633-36.

Yellow fever virus

Four illustrations show the progress of yellow fever in Observations sur la fièvre jaune, faites à Cadix, en 1819, Etienne Pariset and André Mazet, Paris, 1820

https://nihrecord.nih.gov/2019/01/11/nlm-exhibit-yellow-fever-debuts

Yellow fever virus (YFV) vaccines

- A live attenuated YFV vaccine (17D) has been applied safely and effectively for more than 80 years
- One dose of the vaccine can generate long-lasting antibodies, recommendation of booster doses at 10y removed by WHO
- No efficacy studies but protection demonstrated in practice
- Use of fractional doses is safe and effective with 1/5 of a dose resulting in comparable protection for 10 years
  - Temporary solution to vaccine shortages
- Several YF vaccine candidates under development, 3 in clinical trials (inactivated, viral vector, DNA) but would require multiple doses to achieve same level of protective long-lasting immunity

Zurbia-Flores GM et al. Re-thinking yellow fever vaccines. Human vaccines and immunotherapeutics 2023, 18, 1.

Challenges YFV vaccines

- Risk of developing viscerotropic (0.4/100,000) or neurotropic (0.8/100,000) are low but higher risk in persons >60y (1-2/100,000)
- Contraindicated in pregnant/lactating women, infants <6 months, >60y, severe immunodeficiency, hypersensitivity to eggs
- Vaccine produced using traditional manufacturing practices based on propagation of attenuated YFV in chicken embryos
- Vaccine shortages due to emergencies and challenges in scaling up production

Unmet requirement of ~60 million doses remains per annum
1 syringe=1.3 million doses

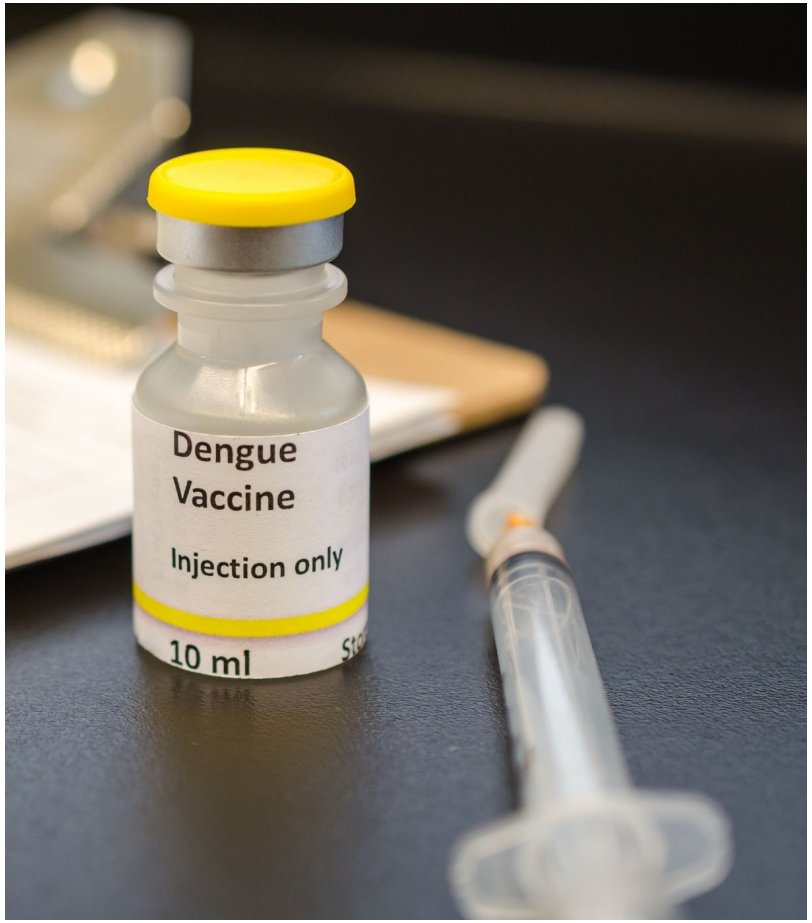
Zurbia-Flores GM et al. Re-thinking yellow fever vaccines. Human vaccines and immunotherapeutics 2023, 18, 1.

Dengue

Chapel converted to hospital ward during dengue outbreak in Honduras

Patients in the corridor of the emergency room in Honduras

Dengvaxia™ (Sanofi)



- Tetravalent live attenuated YFV backbone and four chimeric viruses for four serotypes
- 3 doses 6 months apart
- Increases risk of hospitalization among naïve children (seronegatives)
- Recommended by WHO and ACIP for children with previous dengue (seropositive) living in endemic areas
- Laboratory confirmation of serostatus is required
- Efficacy ~80% for symptomatic disease, hospitalization and severe disease
- Implemented in Puerto Rico with slow take-up

QDENGA (Takeda)

- Tetravalent live attenuated DENV-2 virus backbone and three chimeric viruses expressing E and prM proteins of all four DENV serotypes.
- 2 doses 3 months apart
- Vaccine efficacy is 61% against disease and 84% against hospitalization
- In seropositives protection against all 4 serotypes
- In seronegatives protection against DENV-1 and -2, no efficacy for DENV-3 and no data for DENV-4
- WHO recommended it for children 6-16 years in high transmission areas
- Post licensure studies will be conducted to confirm safety

TV003 (Merck/Butantan Institute)

- Live-attenuated with three full viruses and one chimeric virus for DENV-2 on DENV-4 backbone
- One dose
- Developed by the US National Institutes of Health (NIH)
- Phase 3 trials in Brazil ongoing, 2-year follow-up released
  - Efficacy against symptomatic disease was 89% for seropositives and 73% seronegatives.
  - Higher efficacy for seropositive than seronegative (DENV1 97% and 86%, DENV2 84% and 58%).

Challenges dengue vaccines

- Live attenuated dengue vaccines are 4 vaccines in 1
- Dengue vaccine must protect against all four DENV serotypes to avoid antibody dependent enhancement
- No clear correlate of protection
- A longer period of observation following vaccination is necessary to identify immune enhancement in the context of waning cross-reactive immunity
- Incidence of different serotypes impossible to predict
- Vaccine hesitancy

Closing remarks

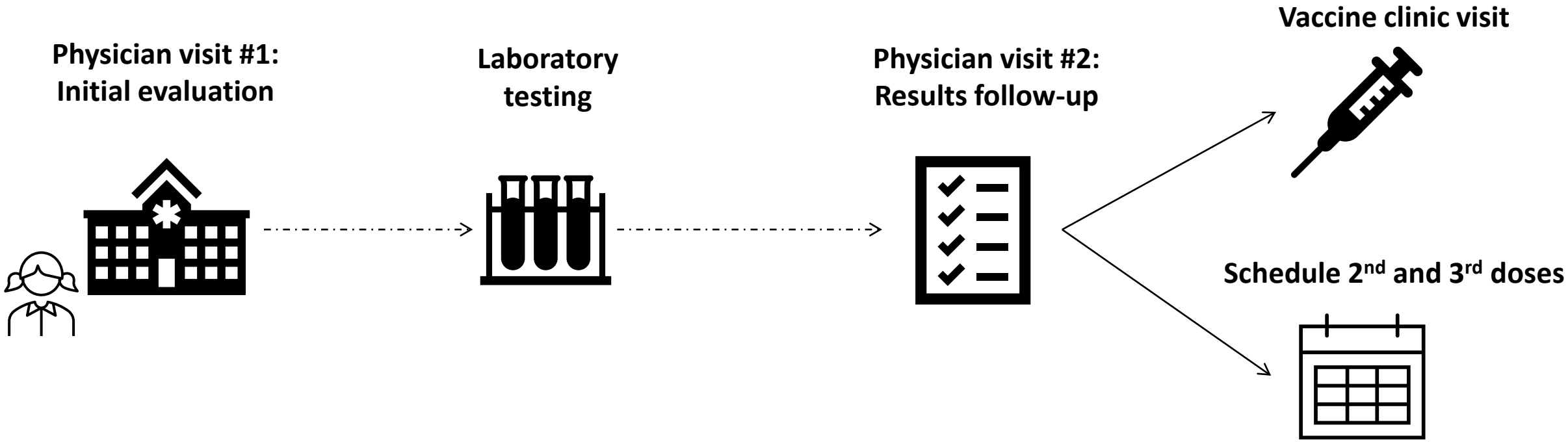
- An ideal vaccine for arboviruses would be single dose, long-lasting protection, high safety profile and produced with cutting edge technology (not traditional manufacturing)
- Vaccine development acceleration technologies are available, but funding has been a major obstacle for development of novel vaccines
- Bringing together public health institutions, government agencies, pharmaceutical companies and non-governmental organizations to establish priorities and have a united purpose
- Vaccine hesitancy and community engagement are key obstacles for vaccine adoption
- Alternative licensing pathways are needed for some vaccines

Acknowledgements

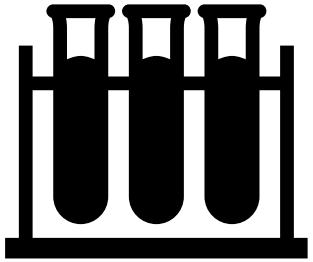
- CDC Dengue Branch
  - Josh Wong
  - Laura Adams

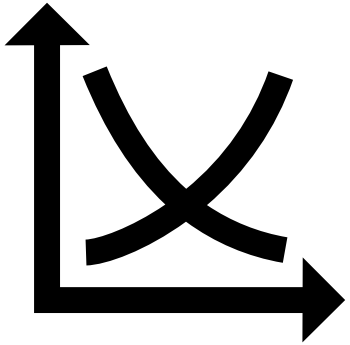
- CDC Arboviral Diseases Branch
  - Susan Hills
  - Erin Staples

Multiple visits to healthcare providers and the laboratory are required to determine eligibility for Dengvaxia ™ and start the series.



Growth Opportunities and Plans for Dengue Vaccine Implementation in PR





Problem	Testing	Physician Clinical Practice	Demand
Action/Plan	• **Single test** for prevaccination screening	• Education provided through **AAP educational activities** • Prevaccination testing **added to preventive services periodicity table**	• **Messaging campaign** starting Q3 2023. • **Increased staff** to conduct local outreach.