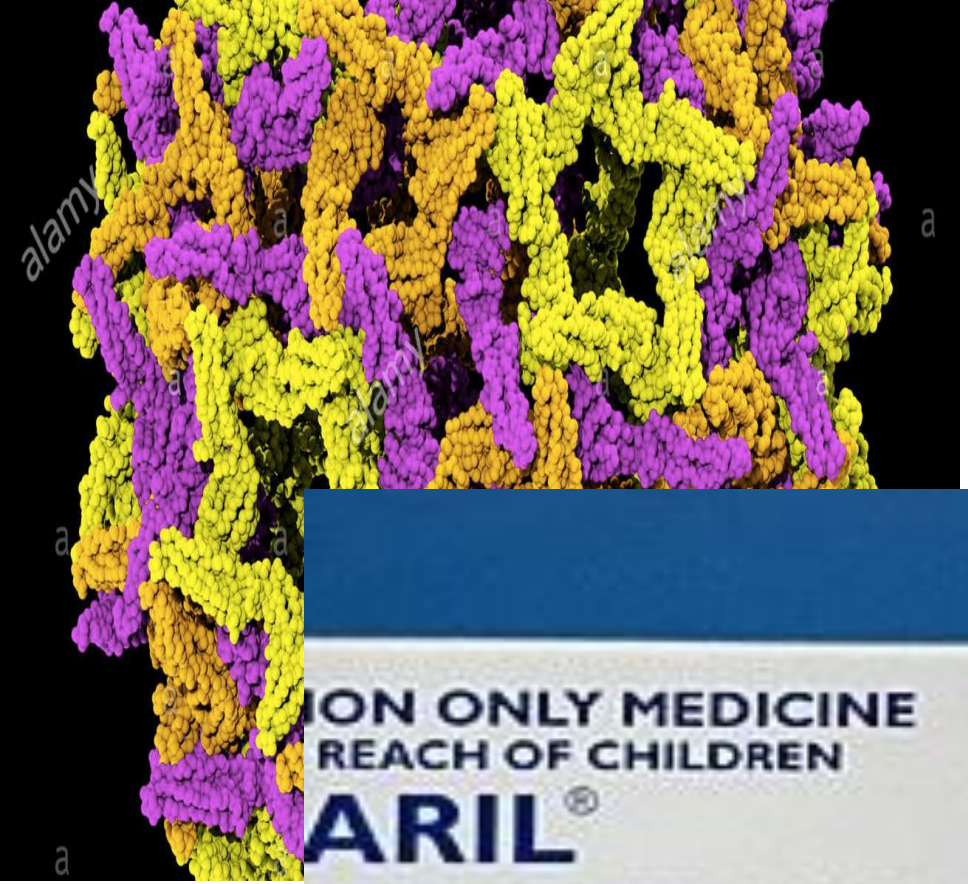
ARBOVIROSIS – VACCINES AND DRUGS

S. BINO

INSTITUTE OF PUBLIC HEALTH

ALBANIA

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WHO position papers

- **Yellow fever** updated in 2013 (2003)
- **Japanese encephalitis** updated in 2015 (2006)
- **Tick borne encephalitis** 2011 (first one)
- **All Dengue** position paper 2016 (first one)

All Flavivirus

WHO dispatched 3.5 million doses of yellow fever vaccine for outbreak response in Brazil – 18.8 milion doses since January 2017

Yellow fever vaccine

- 1937 – Asibi strain - Numerous **mutations in the viral structural and non-structural genes by empirical passage have led to the attenuated variant 17D.**
- **Liive attenuated viral vaccines from the 17D lineage, in tissue culture, principally chicken embryo.**
- Virus with the resulting phenotype is **non-transmissible by mosquitoes**

Yellow fever vaccine

- Single dose (0.5 ml) only and injected either subcutaneously or intramuscularly
- May be administered simultaneously with other vaccines but as per live vaccine sat an interval of 30 days.
- Protection appears to last for life
- The vaccine contains sorbitol and/or gelatine as a stabilizer and is lyophilized.
- Kept at 2–8 °C and reconstituted immediately before use with the sterile diluent provided by the manufacturer.
- After reconstitution, most YF vaccines should be kept on ice, protected from sunlight, and discarded after 1–6 hours or at the end of the vaccination session, whichever comes first.

YF vaccine efficacy

- Large scale YF vaccination have been very effective but where coverage has not been sustained, the disease has recurred.
- 80%–100% of vaccine recipients develop protective levels of neutralizing antibodies within 10 days and 99% do so within 30 days.
- Failure to respond immunologically to YF vaccine associated with HIV infection, pregnancy, and malnutrition

YFV SAFETY

1. Immediate severe hypersensitvity or anaphylactic reactions.
2. YF vaccine associated neurologic disease (YEL-AND) - 0.25–0.8 per 100 000 vaccine doses
3. YF vaccine associated viscerotropic disease (YEL-AVD) - - 0.25–0.4 per 100 000 vaccine doses

YFV WHO recommended strategy

- All endemic countries or areas at risk of YFD should introduce YF vaccine into their routine immunization programmes, giving it to children at age 9– 12 months
- Preventive mass vaccination campaigns are recommended where there is low vaccination coverage.
- Vaccination of travellers

Japanese Encephalitis vaccines

- All of the approximately 15 JE vaccines currently in use are based on genotype 3 virus strains.
- JE vaccines fall into 4 classes:

- inactivated mouse brain-derived vaccines,
- inactivated Vero cell-derived vaccines,
- live attenuated vaccines, and
- live recombinant (chimeric) vaccines.

- Assessment of the population impact of vaccination programs show when high coverage is achieved and sustained in populations at risk of disease, JE in humans can be virtually eliminated
- JE vaccination should be integrated into national immunization schedules in all areas where JE is recognized as a public health priority in at-risk populations
- Recommended strategy:
  - One time campaign in primary target population (typically <15 yearsof age), followed by incorporation into routine childhood immunizationprogram

  - Older groups should be considered for vaccination if disease burden is sufficiently high – HCW etc.

Dengue vaccine

Dengue vaccine

- One dengue vaccine has been registered in several countries.
  - CYD-TDV (Dengvaxia®);
  - Live attenuated (recombinant) tetravalent vaccine
  - Active substances for serotypes 1, 2, 3, and 4.
- Licensed for individuals 9-45 years or 9-60 years of age (depending on license).
- Several other dengue vaccines are in clinical development.

DFV Efficacy and safety

- Based on two Phase 3 trials, the pooled estimate for vaccine efficacy against virologically-confirmed dengue illness of any serotype in the 25 months post-dose 1 (ITT) was 60.3% (95% CI 55.7%–64.5%).
- Vaccine efficacy varied by infecting serotype, previous exposure to dengue, age (which is correlated with previous exposure), and severity.
- Local and systemic adverse reactions following CYD-TDV are comparable to those recorded for other live attenuated vaccines.
- Safety signal of increased risk of hospitalization due to dengue illness in the youngest age group included in clinical trial (2–5 years) in the third year after the first dose (RR of 7.5 (95% CI 1.2–313.8)).

DFV Policy

- CYD-TDV should be administered as a 3-dose series given on a 0/6/12 month schedule
- Countries should only consider introduction of dengue vaccine CYD-TDV in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease.
- To maximize public health impact and cost effectiveness, age groups targeted for vaccination should have 70% or greater seroprevalence.
- Vaccine is not recommended when seroprevalence is below 50% in targeted age group.
- Combined with other measures

TBE vaccines

- Currently there are 4 types of vaccines all based on cell--cultured, formalin-inactivated strains of the TBE virus.
- FSME-.-Immun and Encepur (including FSME-.-ImmunJunior and Encepur-.-Children – Western type – Germany and Austria -1 yo dn beypund
- TBE-.-Moscow and EnceVir, based on the Far-.-Eastern subtype – Russia - 3yo and beyound
- 3 Doses schedule - All TBE vaccines induce an antibody responses considered to be protective in 90% - 100% of vaccinees.

Flavivirus

- **West Nile fever virus** *
- **Tick-borne encephalitis virus** [3 strains] *
- **Dengue viruses types 1–4 (5)** *
- **Japanese encephalitis virus** *
- Omsk haemorrhagic fever virus
- Alkhurma haemorrhagic fever virus
- Rocio virus
- St Louis encephalitis virus
- Zika virus
- Kyasanur Forest disease virus
- **Yellow fever virus** *

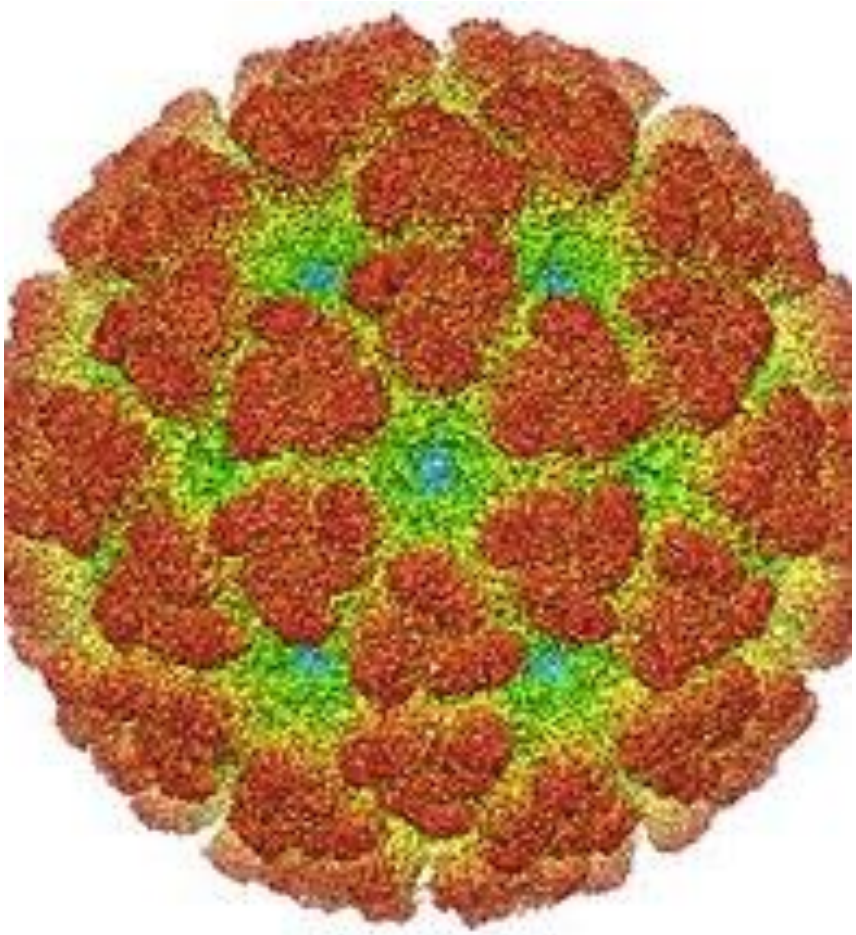
- **New flavivirus vaccination approaches based on YF-17D genomic backbone**

- **WNV**
- **JEV**
- **DENV**

Zika vaccine

- The first of five early stage clinical trials to test the safety and ability of an investigational Zika vaccine candidate called the Zika Purified Inactivated Virus (ZPIV) vaccine to generate an immune system response has already begun
- The experimental ZPIV vaccine is based on the same technology WRAIR used in 2009 to successfully develop a vaccine for Japanese encephalitis.
- The ZPIV vaccine contains whole Zika virus particles that have been inactivated, meaning that the virus cannot replicate and cause disease in humans. However, the protein shell of the inactivated virus remains intact so it can be recognized by the immune system and evoke an immune response.
- WHO/UNICEF Zika Virus (ZIKV) Vaccine Target Product Profile (TPP):Vaccine to protect against congenital Zika syndrome for use during an emergency.

Chicungunia



- Alphavirus genome can be split and a replicon vaccine approach can be used‘
- NIH’s virus-like particle (VLP) vaccine technology for chikungunya. NIH has completed a phase 1 trial, and is presently assessing the vaccine in a phase 2 trial
- - Chikungunya fever vaccine utilizing an insect-specific virus platform - a chimeric virus containing the chikungunya virus (CHIKV) structural proteins.
- Other vaccines

Bunyaviridae

Genus Phlebovirus:
- Sandfly fever virus
- Toscana [3 strains]
- Rift Valley fever virus
- Sever fever thrombocytopenia virus

Genus Nairovirus:
Crimean Congo Haemorrhagic fever virus

Genus Orthobunyavirus:
Tahyna virus
La Crosse virus
Oropouche virus

Genus Hantavirus:
Seoul virus
Dobrava
Hantaan

CCHF vaccine

- No FDA or European approved vaccine or treatment
- Bulgarian vaccine candidate has major disadvantages:
- Requires live CCHF virus
- Crude preparation (non-standardised homogenisation of mouse brain)
- No efficacy studies, no regulatory data package (since 70s)
- Is not acceptable to FDA/MHRA/EMA approval

CCHF - Recombinant approach based on MVA

Modified Vaccinia virus Ankara (MVA)

- Attenuated strain of Vaccinia virus, developed as a smallpox vaccine
- Human safety history: >100,000 doses, no adverse effects reported
- Thermostable – no cold chain required
- Industrial GMP established
- Established regulatory package as Investigational New Drug
- Recombinant MVA in advanced clinical trials (TB, cancer)

Recombinant MVA capability at PHE Porton Down

- Induction of humoral & cellular immunity
- Genome capacity sufficient for large CCHF genes
- Mammalian glycosylation patterns

CCHF MVA-GP vaccine

- Vaccine is based on CCHF glycoproteins expressed in a viral vector.
- CCHF-specific antibodies and T-cells are induced in vaccinated animals of different genetic backgrounds.
- No vaccine-associated pathology.
- 100% protection from disease in a pre-clinical model

CCHF – other approaches

- DNA-based vaccines expressing the CCHFv M segment
- CCHF Virus Like Particles:
- Recombinant tobacco leaves expressing GN and GC
- Inactivated virus from cell culture
- Anti Tick vaccines

DRUGS

Ribavirin

- Licenced and effective drug for Hepatitis C Virus infection
- Used in Yellow fever but ??
- But no action against other flaviviruses [dengue, Omsk haemorrhagic fever, and Kyasanur forest disease)
- Demonstrated in-vitro activity against CCHFV…. in vivo activity some results?

CCHF - Ribavirin

- Effective at inhibiting viral replication of CCHFV in vitro and in vivo
- Approved by the WHO for the treatment of CCHFV infection
- The clinical efficacy of ribavirin in humans remains contested and discussions are mired by inadequate study designs and sample sizes

Favipiravir

- Licenced and effective drug for Influenza Virus infection
- Also (in vitro data) active against:
- • Flaviviruses -West Nile virus, Yellow fever virus,
- • Bunyaviruses - Rift Valley fever virus
- • Alphaviruses - Venezuelan equine encephalitis
- virus Western equine encephalitis virus

Other

- Monoclonal antibody approaches
- Polyclonal antibody approaches - Antibody production in sheep – ovine polyclonal