Flavivirus vaccines: policy and market considerations

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Indication for currently licensed flavivirus vaccines – neuroinvasive

- **Japanese encephalitis (JE) vaccine recommendations**
  - Children in endemic areas as part of routine childhood program
  - Travelers to endemic areas with extensive outdoor exposure during transmission season

- **Tick-borne encephalitis (TBE) vaccine recommendations**
  - Individuals aged ≥1 year in highly endemic areas (i.e., average incidence ≥5 cases/100,000 population per year)
  - High-risk individuals where disease has moderate or low incidence (i.e., average <5/100,000)
  - Travelers to endemic areas with extensive outdoor activities during transmission season
Indication for currently licensed flavivirus vaccines – hemorrhagic

- Yellow fever (YF) vaccine recommendation
  - Individuals aged ≥ 9 months living in or traveling to at-risk area

- Dengue (DEN) vaccine recommendations
  - Dengvaxia (SP): Persons living in endemic areas with documented preexisting immunity aged 6-45 years (EMA) or 9-16 years (USA)
  - Qdenga (Takeda): Persons aged ≥4 years (EMA) or 4-60 years (Brazil, Indonesia) regardless of past dengue virus infection*

- Kyasanur Forest Disease (KFD) vaccine recommendation
  - Persons aged 7–65 years in endemic areas in Karnataka state, India

*Under review at WHO/SAGE and CDC/ACIP
Dosing schedules of current flavivirus vaccines

**YF**
- One dose at ≥ 9 mo provides life-long protection for most individuals

**JE**
- Two doses at 4-week intervals of inactivated vaccine at ≥ 6 mo
- One dose of live attenuated at ≥ 8 mo or live recombinant at ≥ 9 mo

**DEN**
- Dengvaxia – three doses at interval of 6 months
- Qdenga – two doses at 0 and 3 months

**TBE**
- Three doses at 1-3 months interval for first two doses, 5-12 mo between 2nd and 3rd doses
- Booster doses at 3-5 years for those who continue to be at risk

**KFD**
- Three doses at 1 month interval for first two doses, 6-9 mo between 2nd and 3rd doses
- Booster doses annually if remain at risk

*mo=months old*
Potential indications for new flavivirus vaccines

- West Nile virus (WNV) vaccine likely to target older adults in areas with increased incidence of disease
  - Analysis found this strategy most cost beneficial and could reduce WNV neuroinvasive disease cases by 30% and deaths by 60% in U.S. annually*

- Zika virus (ZIKV) vaccine TTP updated February 2017†
  - Outbreak response target woman of reproductive age (9 to 49 years) and potentially males of same age
  - Endemic areas target children aged ≥ 9 months and adults in first universal campaign followed by routine program

- Dosing schedule will be determined by vaccine platform and immunogenicity in target population

†TTP- target product profile: https://www.who.int/publications/m/item/who-unicef-zika-virus-(zikv)-vaccine-target-product-profile-(tpp)
Other considerations for vaccine policy

- Robust and sustained immunity desirable to prevent vertical transmission for ZIKV; need for booster doses will influence use and uptake

- Increased safety concerns for vaccines could preclude their use in key target populations (e.g., pregnant women, older adults)

- International Health Regulations might need to be adapted for new generation YF vaccine

- Co-administration data with other childhood vaccines or sequential administration data with other flavivirus vaccines needed
  - Examine for potential immunologic interference*
  - Address safety concerns regarding antibody dependent dependent enhancement†

Cost and marketing considerations
Costs of vaccine vary considerably

- Most childhood vaccines are relatively inexpensive particularly if procured through UNICEF or national programs (e.g., vaccines for children, VFC)

- UNICEF cost range based on manufacturer, time on market, and demand
  - Low cost vaccines $0.10 - $1.50/dose (BCG, DT, DTP, IPV, Penta, HepB, JE, MR, Men, Rota, Td, Typhoid, YF)
  - Mid cost vaccines $1.51 - $10.00/dose (COVID, HepA, HPV, MMR, Cholera, PCV, Rabies)
  - High cost vaccines $98.60/dose (Ebola)

- VFC costs for Dengvaxia $95.93/dose or $288/series; HPV $225/dose

- Cost for vaccines for U.S. travelers range up to $1125/series
Marketing considerations and challenges for flavivirus vaccines

- Cost of vaccines is driven by demand
  - Demand impacted by competing priorities, disease awareness, and vaccine hesitancy

- Often limited number of manufacturers for one vaccine
  - Problems with manufacturing can result in limited to no vaccine supplies (e.g., KFD vaccine)
  - Outbreaks can quickly deplete available vaccines (e.g., YF vaccine in 2016-2017)

- Flavivirus vaccine market has several challenges
  - Research and development gaps, regulatory barriers, manufacturing limitations, unpredictable country demand, and vaccine uptake
Summary of policy and marketing considerations

- Current flavivirus vaccine policies likely to influence new vaccine policy
- mRNA vaccines provide opportunity to optimize prevention of flaviviral diseases by addressing gaps
- Challenges to change or adapt current flavivirus vaccines with robust immune response and low cost
- Flexibility for new flavivirus vaccines with variable price points
- Commitment of governments, manufacturers, and international partners needed to support flavivirus vaccine development and use to reduce disease morbidity and mortality