Japanese encephalitis and Japanese encephalitis vaccine

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Anthony A Marfin, MD, MPH, MA
Center for Vaccine Innovation and Access
PATH
Outline

• Japanese encephalitis: Virus, disease, and epidemiology
• Japanese encephalitis vaccines
• Past decade of expanded JE control
• Challenges over the next decade
JE: Virus

- Flavivirus (30+ human pathogens)
- Five JEV genotypes
- Japanese encephalitis serocomplex
  - 11 closely related flaviviruses
  - Mosquito-borne viruses that primarily infect and replicate in birds
  - JE, WNV, SLE, ROC, MVE, KUN, & USU viruses can cause human encephalitis
- JEV distantly related to YF, Zika, and dengue viruses; very different epidemiology
  - JEV no human-to-human transmission
  - JEV not transmitted by *Aedes aegypti*
  - Do not see explosive JE outbreaks as seen in YF, Zika, and dengue
Old world distribution of four viruses in the Japanese encephalitis serocomplex
JE: Disease

- < 1% JEV-infected persons develop encephalitis
  - Brain inflammation & swelling
  - Seizures, confusion, coma, paralysis
  - Respiratory failure
  - No specific anti-viral treatment
- Outcome
  - 20-30% die
  - 30-50% survivors→severe, life-long neuro deficits
- As many as 7 million JEV infections per year
  - Risk factors for progression to encephalitis unknown
  - Cannot target vaccination to specific at-risk groups
- Many other viral, toxic, & auto-immune causes of encephalitis
JE: Epidemiology / epizootology

- Before widespread vaccination in late 1980s, estimated 70K JE cases/year
- Zoonotic disease
  - Ongoing JE virus transmission even when no human cases identified
- Variable disease patterns
  - Temperate: Large, seasonal outbreaks
  - Tropical: Year-around transmission with periodic outbreaks
- Rural disease, associated with flooding rice irrigation
  - Maintenance/reservoir/amplifying hosts: Egrets, herons, bitterns
  - Vector: *Culex tritaeniorhynchus* and related species that breed in rice paddies
  - Amplifying hosts: Swine (NB: Do not need swine for hyperendemic transmission)
- 3B people in 24 JE-endemic countries in So Asia, SE Asia, China, & Western Pacific
Transmission cycle of Japanese encephalitis and West Nile viruses
Japanese encephalitis vaccines

• > 15 vaccines used; 4 production methods
  o Mouse brain-derived, inactivated (first public health vaccine); VE: 91-93%
  o Vero cell culture-derived, inactivated
  o Live chimeric
  o Live attenuated (most widely-used public health vaccine); VE: 99%
• Several JEV genotype III strains used (e.g., SA 14-14-2, Beijing, Karnataka, Nakayama)
• 3 WHO-prequalified JE vaccines
  o Biological E – JEEV (Vero-cell derived, inactivated)
  o Thai GPO-MBP – IMOJEV (live chimeric)
  o Chengdu Institute of Biological Products – SA 14-14-2 (live attenuated)
• Gavi has only supported procurement of SA 14-14-2 for new vaccine introduction
JE vaccine: Mechanisms and correlates of protection

- All 4 JEVs elicit neutralizing antibodies (NAb) to E & prM proteins
  - T-cell independent response
  - Correlate of protection: PRNT\textsubscript{50} ≥ 1:10 (from mouse challenge studies)
  - For vaccine studies, end-points are seroprotection, serovconversion, GMTs (based on PRNT)
- For durable & complete immunity, viral replication needed → CMI/innate immune responses
  - CD4\textsuperscript{+} T-cell clonal proliferation in response to E and NS proteins
  - CD4\textsuperscript{+} T-cell important in long-term anamnestic response
  - CD4\textsuperscript{+} T-cell response positive prognostic indicator for encephalitis outcome
  - ↑ α, β, γ IFN in response to dsRNA/NS proteins limits early replication and stop progression

\cite{Hegde2017}

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JE vaccine: Cost-effectiveness

- With only 70K JE cases per year in all of Asia, how can vaccine be cost effective?
  - Most illnesses/deaths in u15 children
  - Life-long, severe neuro deficits in people that ill live 50-60 more years
- Many JE vaccine CEAs in LICs (generally favorable for vaccination)
- As more Asian countries become MICs, does cost effectiveness change?
- 2019: JE vaccine CEA, Philippines
  - Using cost of acute illness (COI), JE vaccination cost effective
    - 1 DALY averted costs $29-$265 (up to 9% of per capita GDP)
  - Using full treatment cost incl. long-term rehab cost, JE vaccine becomes cost saving
    - ↑ health care costs & social expectations regarding long-term care and rehab of survivors will ↑ treatment costs in MICs, making vaccines more cost effective/cost saving
JE vaccine: Impact

- Measure actual reduction in JE after vaccine introduction
- 2006-2011: JE vaccination campaigns in 31 Nepal districts\(^1\)
- Review 2004-2014 JE and AES data
- Post-campaign JE incidence rate: 0.7 cases/10\(^5\)
  - 78\% (95\% CI 76\%-79\%) reduction in JE incidence
  - Through 2014, est. 2,900-3,100 JE cases prevented
- Post-campaign AES incidence: 5.5 cases/10\(^5\)
  - 59\% (58\%-60\%) reduction in AES incidence
  - Through 2014, est. 9,300-9,600 AES cases prevented
- Reduction in AES? JE actually makes up much larger fraction of AES than suspected

JE vaccination, where were we in 2009?

- Among 24 JE-endemic countries:
  - Geographically-targeted programs: Malaysia, Australia (2)
  - Within national immunization program (NIP): Japan, ROK, Thailand (3)
  - Limited distribution: China, India, Nepal, Sri Lanka, & Vietnam (5)
  - Program not necessary based on surveillance data: Singapore (1)
  - No programs: Bangladesh, Bhutan, Cambodia, Indonesia, Lao PDR, Myanmar, Pakistan, PNG, Philippines, Russia, Timor Leste, DPRK, Brunei (13)

*Japanese Encephalitis Morbidity, Mortality, and Disability: Reduction and Control by 2015*
JE vaccination, where are we in 2019?

- Among 24 JE-endemic countries:
  - Geographically-targeted programs: DPRK, Australia, Malaysia (3)
  - Within NIP: Japan, ROK, Thailand, Cambodia, Lao PDR, Myanmar, Indonesia, Philippines (8)
  - Expanded JE vaccination program since 2009: China, India, Nepal, Sri Lanka, & Vietnam (5)
  - Program not necessary based on surveillance data: Singapore (1)
  - Expanded JE surveillance: Bhutan, Pakistan (2)
  - No programs: Bangladesh, PNG, Russia, Timor Leste, Brunei* (5)

10 countries introduce/expand JE vaccination with assistance of Gavi, WHO, SEARO, WPRO, US CDC, UNICEF, BMGF, MA Cargill Philanthropies & PATH

2 countries expand JE surveillance with assistance of SEARO, US CDC & PATH

*ad hoc vaccination campaigns in response to outbreaks
JE Experts Meeting, Seattle, August 2018

- Booster dosing
- Urban JE transmission
- JE in previously vaccinated persons
  - Waning immunity in persons
  - New or emerging JEV genotypes
- Serious disease in recently vaccinated persons
  - Vaccine-associated encephalitis (AEFI)
  - Live vaccines and possible reversion to virulence
- New JE-endemic areas
- Emerging vaccine hesitancy
  - Parental/governmental mistrust of new vaccines
  - Fewer severe JE cases, parents less convinced of need for JE vaccine
Boosting policy needs clarity

- Decisions about booster affect vaccine delivery costs, cold chain storage, supply-demand, etc.
- What are current boosting policies for WHO-prequalified vaccines?
  - **JEEV**: Adults with continuous JE risk should get booster
    - **IXIARO**: Children or adults should be boosted if there is ongoing JE exposure
  - **IMOJEV**: u18 children should be boosted if long-term protection is required
  - **SA 14-14-2**: For programmatic purposes, a booster dose at 2 years of age may be recommended
  - **WHO (2015)**: Need for a booster dose in endemic settings not established for any JE vaccine other than mouse brain-derived vaccines
- Clinical studies of waning immunity and boosting with IMOJEV\(^a\) and SA 14-14-2\(^b\)
  - Previously immunized children with no measurable NAb years after primary have strong anamnestic response within 7d of booster
  - Is this immunologic recall rapid enough to protect against infection?

\(^b\) Preliminary results of PATH JEV07, 4-year follow-up study of Bangladeshi children
Urban JE transmission

- Historically, JEV transmission associated with rural settings and rice irrigation
- Interface of rice production & urban sprawl, new opportunities for human infection?

Can Tho City, major urban area in Vietnam’s Mekong Delta, ~1.6 million people
- JEV infection of pigs and presence of JEV in mosquitoes within urban Can Tho City
- Human cases acquired in Beijing, Karachi, Hong Kong, and Delhi reported
- Although JE considered rural disease, must watch for ↑ urban transmission

**Circulation of Japanese Encephalitis Virus in Pigs and Mosquito Vectors within Can Tho City, Vietnam**

Johanna F. Lindahl¹, Karl Ståhl², Jan Chirico³, Sofia Boqvist², Ho Thi Viet Thu⁴, Ulf Magnusson¹*

2013 PLoS Neglected Tropical Diseases
Thank you. Questions?

Anthony A Marfin
aamarfin@path.org