Japanese encephalitis and Japanese encephalitis vaccine

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Photo: PATH/Rocky Prajapati

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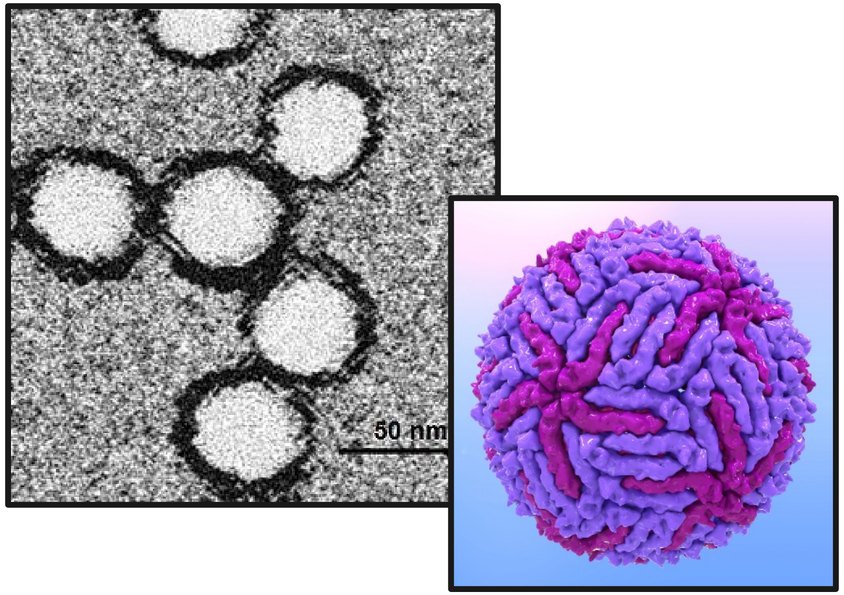
Outline

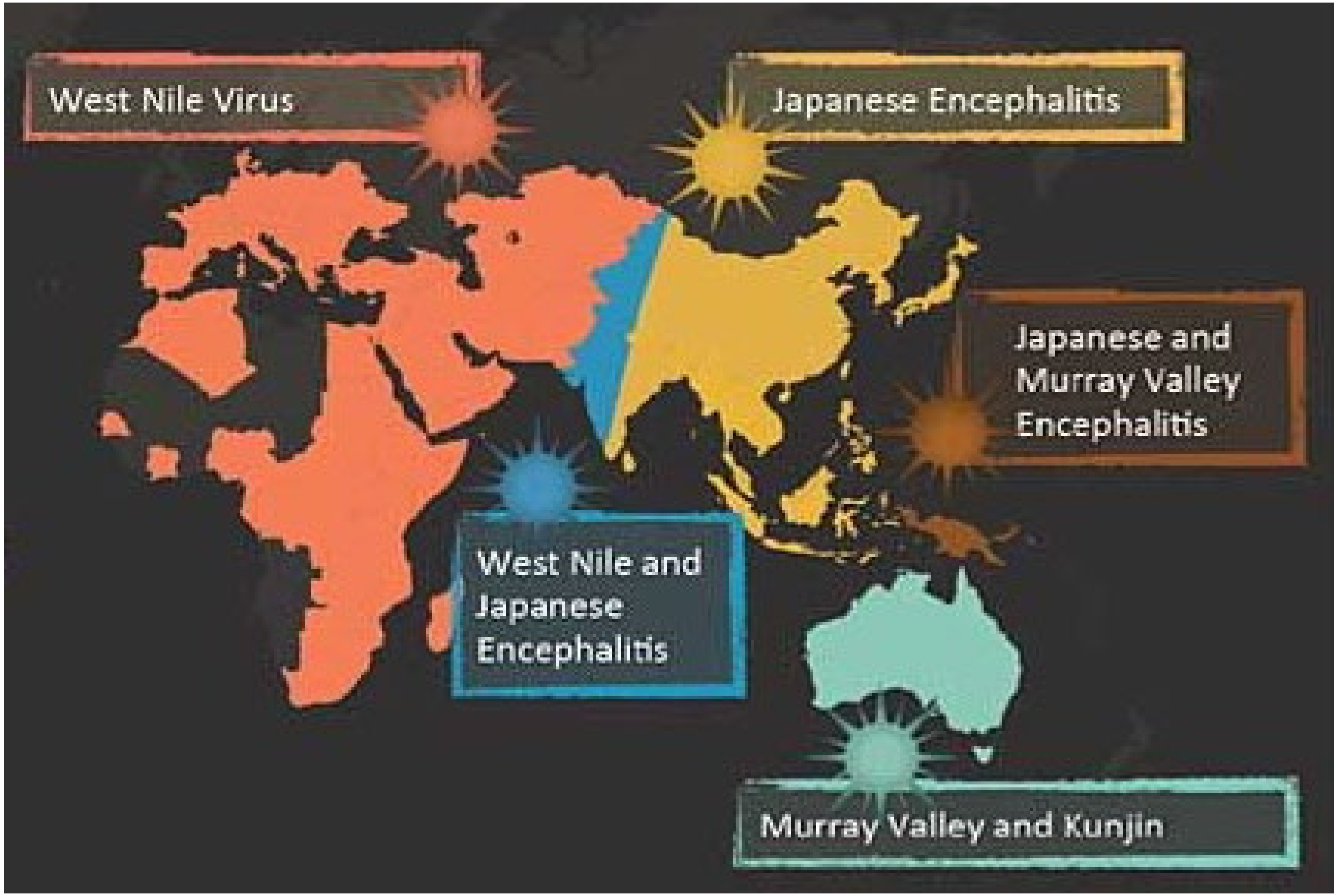
- Japanese encephalitis: Virus, disease, and epidemiology
- Japanese encephalitis vaccines
- Past decade of expanded JE control
- Challenges over the next decade

JE: Virus



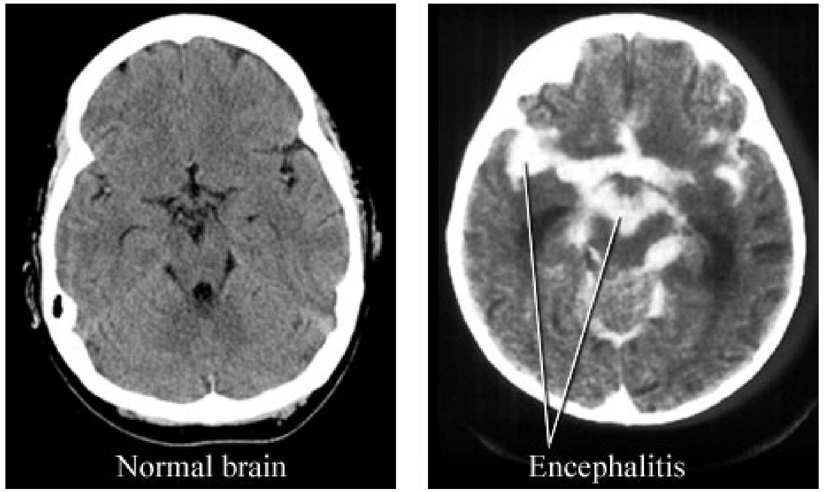
- Flavivirus (30+ human pathogens)
- Five JEV genotypes
- Japanese encephalitis serocomplex
  - 11 <u>closely</u> related flaviviruses
  - Mosquito-borne viruses that primarily infect and replicate in birds
  - JE, WNV, SLE, ROC, MVE, KUN, & USU viruses can cause human encephalitis
- JEV distantly related 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

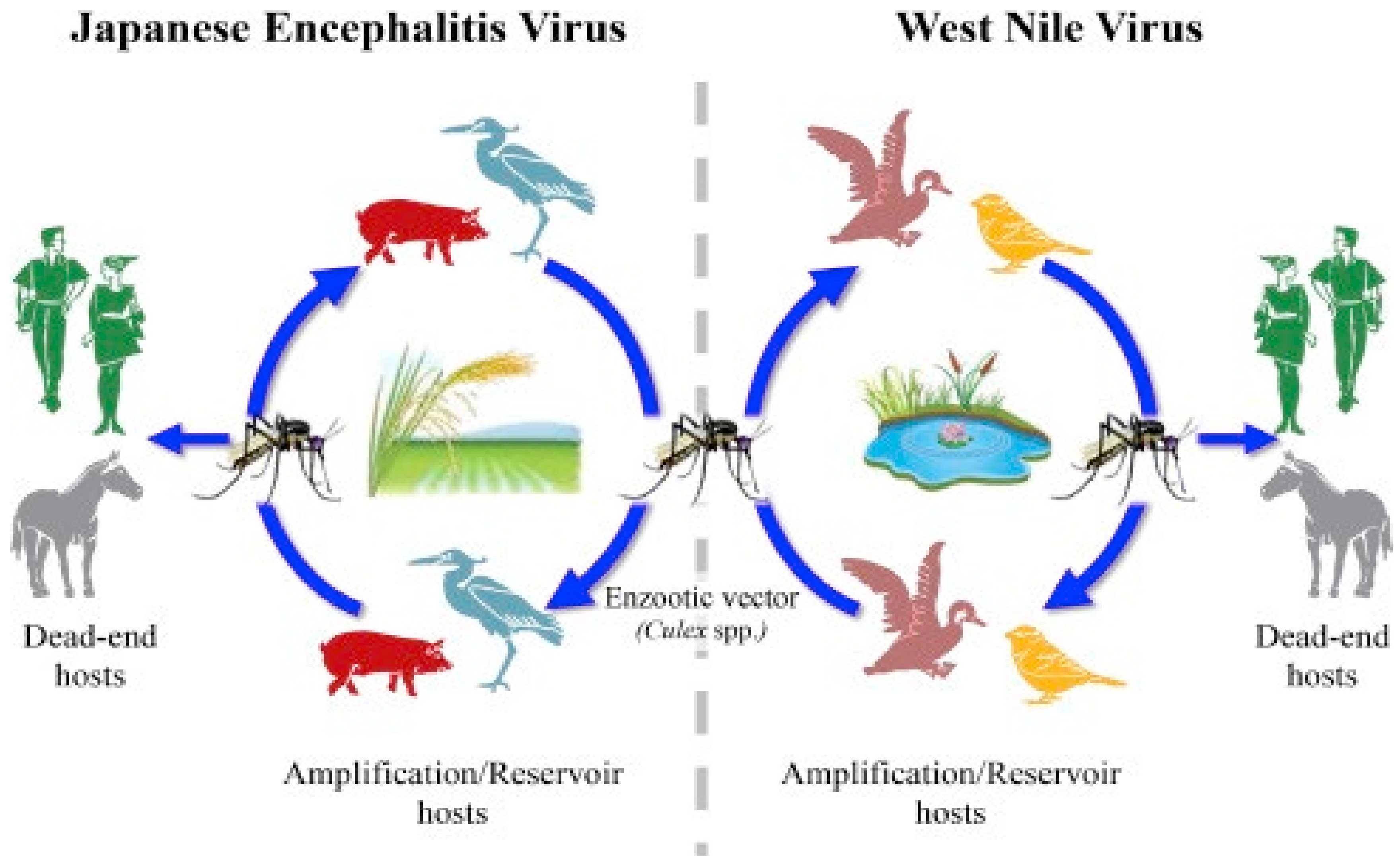
- < 1% JEV-infected persons develop encephalitis
  - Brain inflammation & swelling
  - Seizures, confusion, coma, paralysis
  - Respiratory failure
  - No specific anti-viral treatment
- Outcome
  - 20-30% die
  - 30-50% survivors→severe, life-long neuro deficits
- As many as 7 million JEV infections 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
  - Mouse brain-derived, inactivated (first public health vaccine); VE: 91-93%
  - Vero cell culture-derived, inactivated
  - Live chimeric
  - 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
  - Biological E – **JEEV** (Vero-cell derived, inactivated)
  - Thai GPO-MBP – **IMOJEV** (live chimeric)
  - 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

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JE vaccine: Mechanisms and correlates of protection[1]

- All 4 JEVs elicit neutralizing antibodies (NAb) to E & prM proteins
    - T-cell independent response
    - Correlate of protection: $PRNT_{50} \geq 1:10$ (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
    - $CD4^{+}$ T-cell clonal proliferation in response to E and NS proteins
    - $CD4^{+}$ T-cell important in long-term anamnestic response
    - $CD4^{+}$ 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

[1] Hegde NR, Gore MM. encephalitis vaccines: Immunogenicity, protective efficacy, effectiveness, and impact on the burden of disease. Hum Vaccin Immunother. 2017 Jun 3;13(6):1-18.

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

[1] Upreti SR et al. PLoS Negl Trop Dis. 2017;11(9):e0005866.

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?

[a] Feroldi E et al 2013. Human Vaccines & Immunotherapeutics 9:4, 889–897.
[b] Preliminary results of PATH JEV07, 4-year follow-up study of Bangladeshi children

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Urban JE transmission

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

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

Johanna F. Lindahl[1], Karl Ståhl[2¤], Jan Chirico[3], Sofia Boqvist[2], Ho Thi Viet Thu[4], Ulf Magnusson[1*]

- 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 <u>in</u> Beijing, Karachi, Hong Kong, and Delhi reported
- Although JE considered rural disease, must watch for ↑ urban transmission

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Thank you. Questions?

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