Rationale to include Japanese encephalitis among diseases qualifying under FDAAA section 524

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NOVARTIS

Conflicts of Interest

- Novartis is a marketing and distribution partner of Intercell, licensing applicant for an inactivated JE vaccine
- Consultant
  - PATH (Program for Appropriate Technology in Health) – to promote implementation of JE vaccination in developing Asian countries

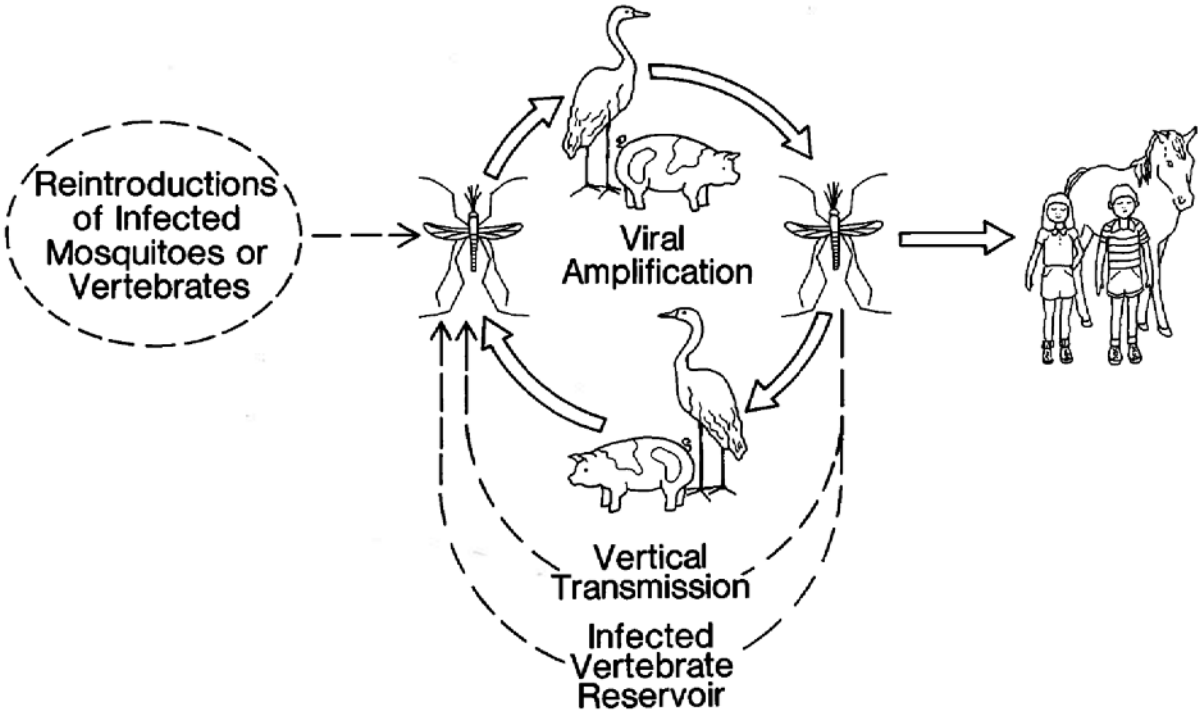
Qualifying criteria for tropical disease applications under section 524

Product for prevention or treatment of

- Listed neglected tropical diseases
- Other infectious disease for which
  - There is no significant market in developed nations
  - That disproportionately affects poor and marginalized populations

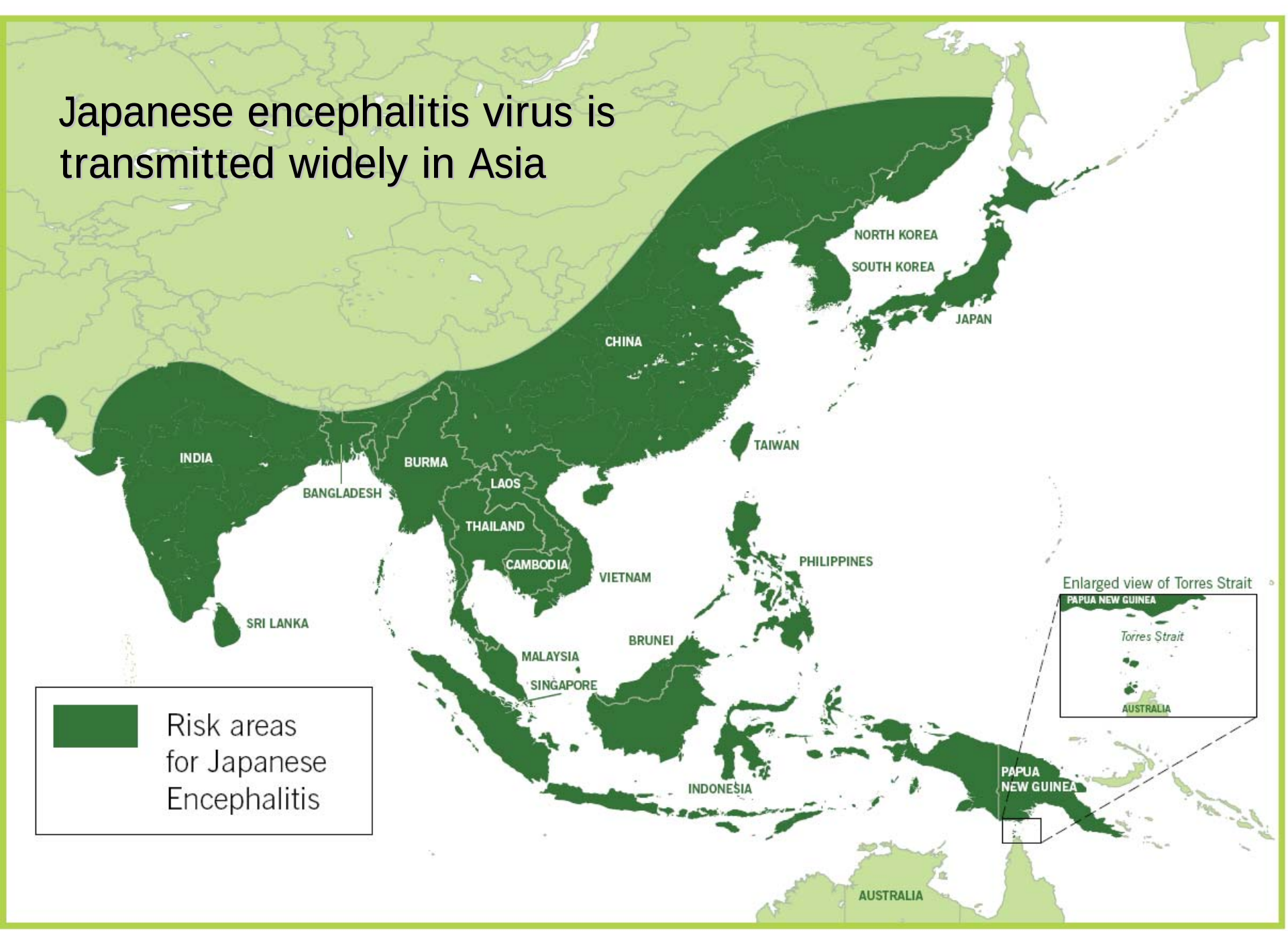
Japanese encephalitis viral transmission cycle

- **Mosquitoborne flaviviral encephalitis**
- **Humans are infected incidentally – dead-end hosts**
- **Disease cannot be eradicated**
- **Human vaccination is the only effective means for control**



Tsai TF in Plotkin SA, Mortimer EA eds. Vaccines 2nd ed. 1998.

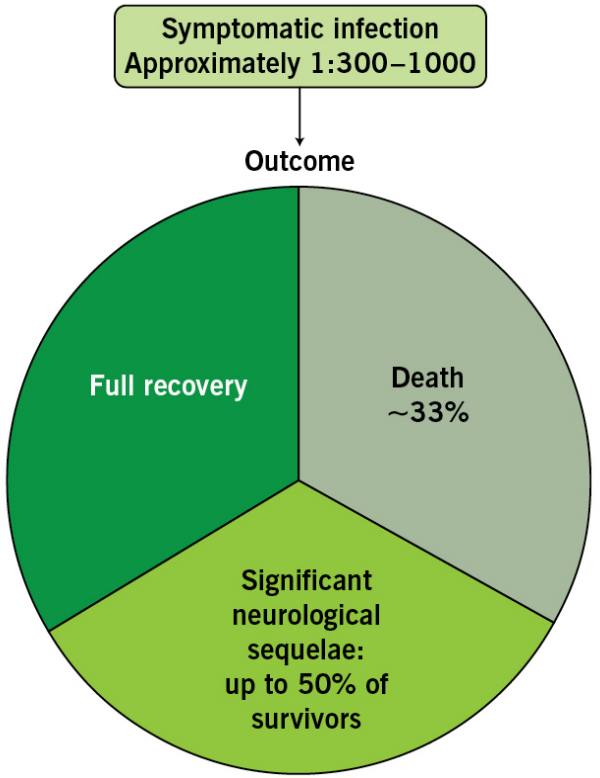
Japanese encephalitis virus is transmitted widely in Asia



Japanese encephalitis can have devastating clinical consequences

- Between 1 in 300 and 1 in 1000 infections lead to clinical disease[1-2]
- Acute encephalitis that is fatal in ~**30%** of cases[4-7]
- Up to **50%** of survivors have persistent neurological sequelae[5,6]
- No specific therapy is available

Summary of outcomes of JE infection



Adapted from references 1-8

1. Grossman RA et al. Am J Epidemiol 1973; 98: 133-149. **2.** Southam CM. J Infect Dis 1956; 99: 163-169. **3.** Umenai T et al. Bull World Health Organ 1985; 63: 625-631. **4.** Burke DS et al. Am J Trop Med Hyg 1985; 34: 1203-1210. **5.** Hoke CH et al. J Infect Dis 1992; 165: 631-637. **6.** Schneider RJ et al. Southeast Asian J Trop Med Public Health 1974; 5: 560-568. **7.** Simpson T & Meiklejohn G. Am J Trop Med Hyg 1947; 27: 727-731.

Japanese encephalitis: long-term neuropsychological sequelae contribute to a hidden burden of disease

- **6-27 year follow up (~15y) and case-control study of JE cases, Shanghai**
- **22% had a neurological deficit - OR 6.30, 95% CI, 1.24-31.9 vs. non-JE cases**
- **18% were severely retarded; 6% were incapacitated in activities of daily living**

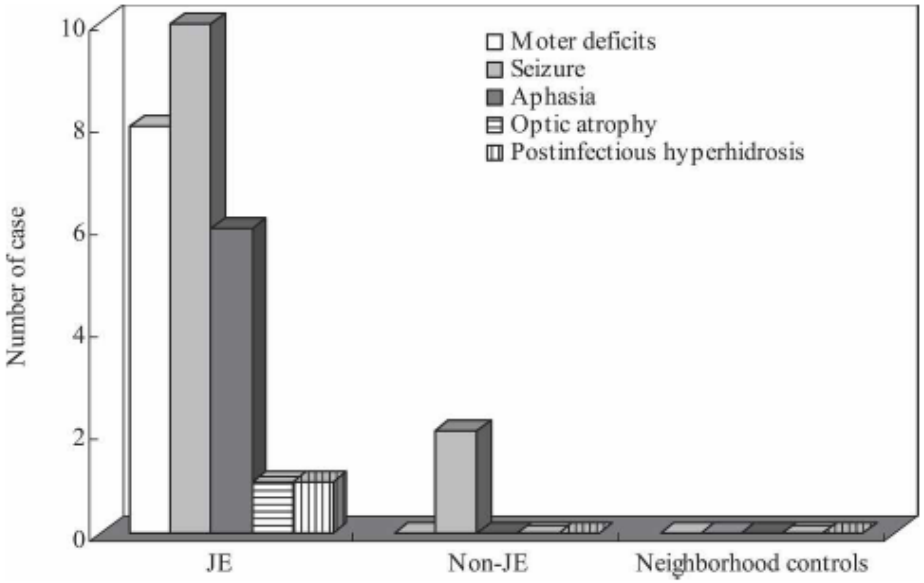


FIGURE 2. Neurologic deficits in JE and non-JE encephalitis cases 6–27 years after index hospitalization compared with findings in normal controls.

Neurologic abnormalities, cognitive function, and ADL scores at follow-up of JE patients, post–non-JE encephalitis patients, and neighborhood controls

Examination	JE (N = 78)	Post–non-JE encephalitis (N = 71)	Neighborhood control (N = 78)
Abnormal neurologic findings (%)	17 (21.8)	2 (2.8)‡	0 (0)‡
MMSE§ score < 21 (%)	8 (10.3)	1 (1.4)*	0 (0)†
IQ#			
> 84 (%)	43 (55.1)	52 (73.2)‡	66 (84.6)‡
70–84 (%) 28%	6 (7.7)	1 (1.4)	1 (1.3)
< 70 (%) 18%	11 (14.1)	0 (0)	0 (0)
ADL			
< 21 (%)	66 (84.6)	71 (100)†	78 (100)‡
21–60 (%)	7 (9.0)	0 (0)	0 (0)
61–80 (%)	5 (6.4)	0 (0)	0 (0)

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$ for comparison of cited group with the JE group.
§ MMSE, Mini-Mental State Examinations. IQ was determined for 60 JE and 53 post non-JE encephalitis patients and for 67 neighborhood controls.

Ding D et al. Am J Trop Med Hyg; 2007; 77:528-33.

JE is a significant cause of morbidity and mortality throughout Asia

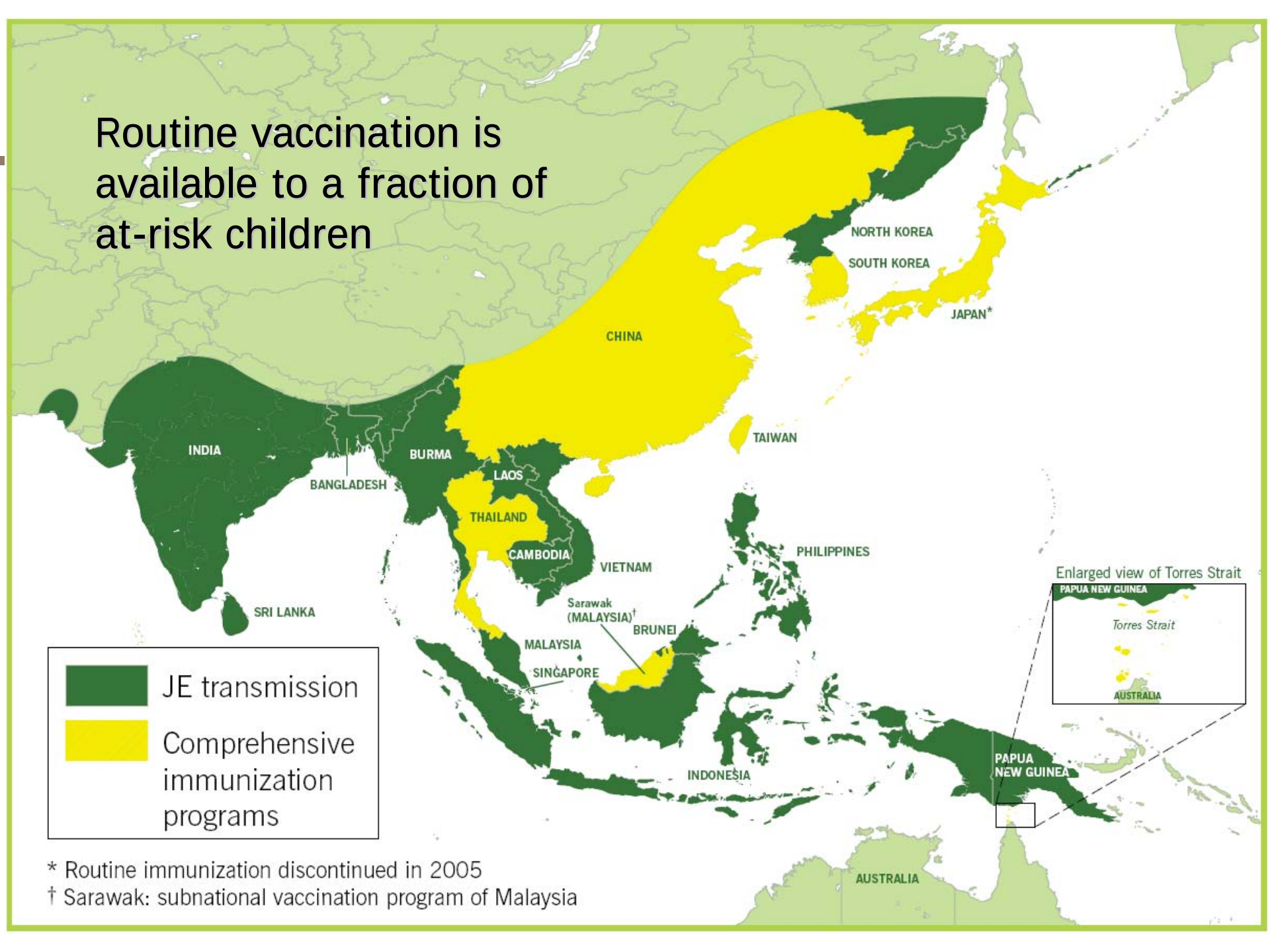
~30,000 cases/year ~10,000-15,000 deaths/year

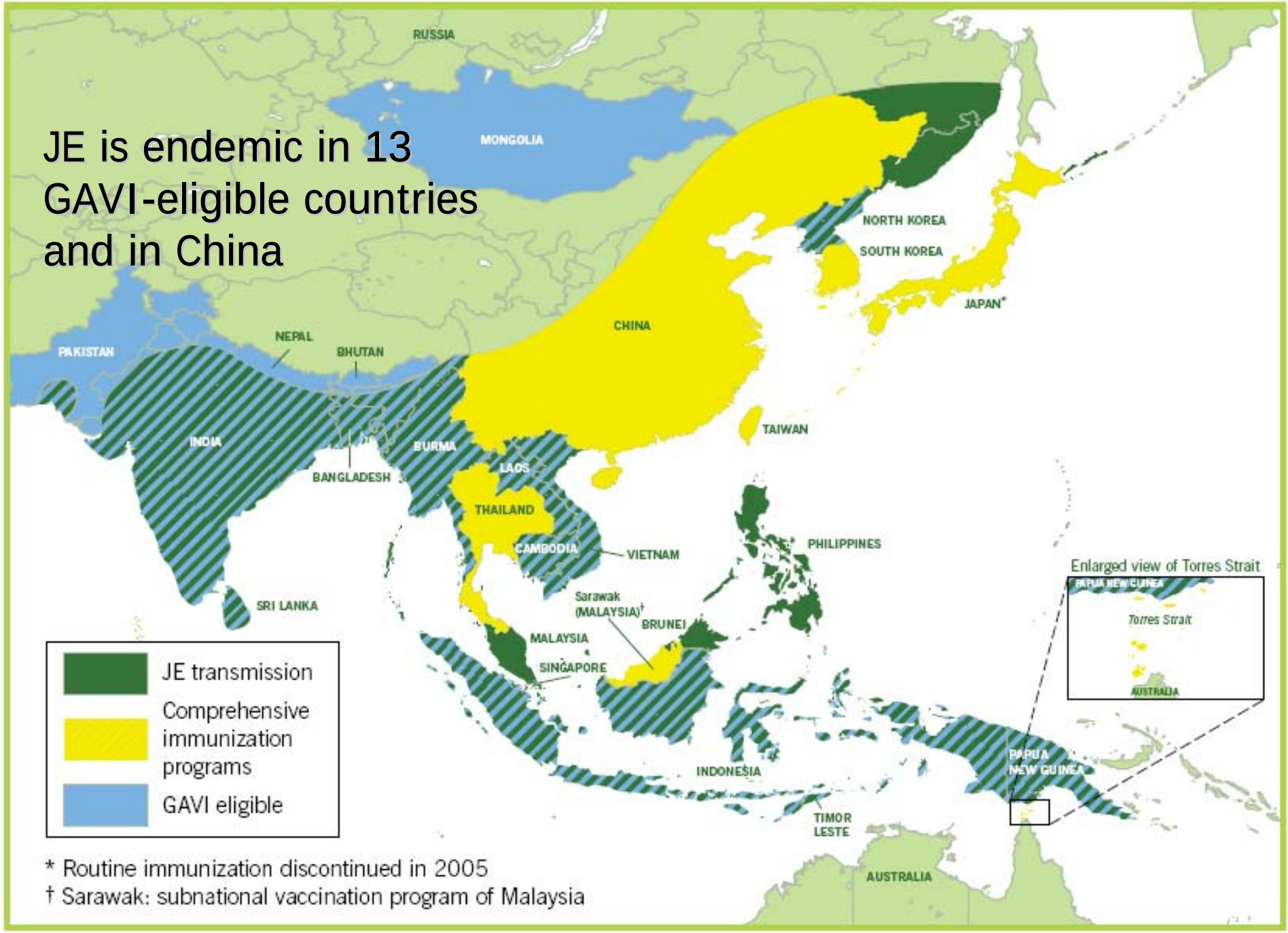
Country	Total deaths	Deaths/100,000	Total DALYs	DALYs/100,000
Bangladesh	700	0.5	24,000	17
Cambodia	100	0.7	4000	32
PR China	2500	0.2	281,000	22
India	6900	0.7	226,000	22
Indonesia	200	0.1	23,000	11
Japan	0	0	0	0
North Korea	100	0.5	6000	28
South Korea	NA	NA	6000	13
Lao PDR	100	2.3	5000	84
Malaysia	0	0	2000	9
Myanmar	400	0.7	13,000	27
Nepal	200	0.7	5000	22
Pakistan	2400	1.6	82,000	55
Papua New Guinea	100	1	2000	41
Philippines	NA	NA	8000	10
Singapore	Na	NA	260	6
Sri Lanka	Na	NA	1000	7
Thailand	Na	NA	5000	8
Vietnam	200	0.2	11,000	14
Totals	13,900	-	699,260	-

Data for 2002. DALYs: disability-adjusted life years

1. Adapted from World Health Organization. Global Burden of Disease 2002 Estimates for the World Health Report 2004

Routine vaccination is available to a fraction of at-risk children




JE is endemic in 13 GAVI-eligible countries and in China
RUSSIA
MONGOLIA
NORTH KOREA
SOUTH KOREA
JAPAN*
CHINA
PAKISTAN
NEPAL
BHUTAN
INDIA
BURMA
BANGLADESH
LAOS
THAILAND
TAIWAN
CAMBODIA
VIETNAM
PHILIPPINES
SRI LANKA
Sarawak (MALAYSIA)†
BRUNEI
MALAYSIA
SINGAPORE
INDONESIA
TIMOR LESTE
PAPUA NEW GUINEA
AUSTRALIA
Enlarged view of Torres Strait
PAPUA NEW GUINEA
Torres Strait
AUSTRALIA
JE transmission
Comprehensive immunization programs
GAVI eligible
* Routine immunization discontinued in 2005
† Sarawak: subnational vaccination program of Malaysia

JE incidence is highest in rural areas

- *Cx tritaeniorhychus* are abundant in rural areas
- Larval stages are adapted to rice paddies
- Adults feed on pigs, other vertebrates.

Inequity in healthcare, China

Rural populations disproportionately have been left out of healthcare gains

- Improved life expectancy has been slower to occur in poor than in rich provinces
- Child mortality rates remain higher in rural than in urban areas

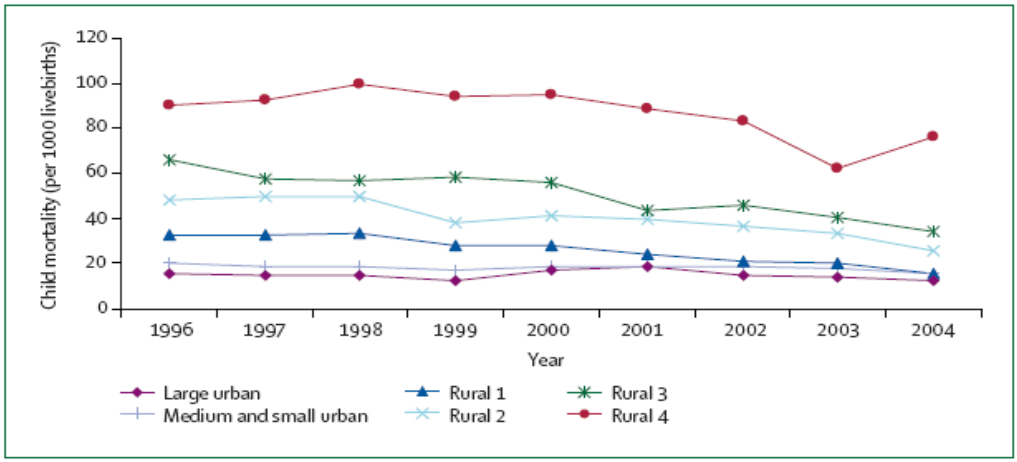


Figure 4: **Trends in mortality in children age less than 5 years by socioeconomic conditions of areas of residence, 1996–2004[10]**

Rural 1=most affluent rural. Rural 2=better-off rural. Rural 3=poor rural. Rural 4=poorest rural. Rating based on a deprivation index combining socioeconomic indicators of the areas.

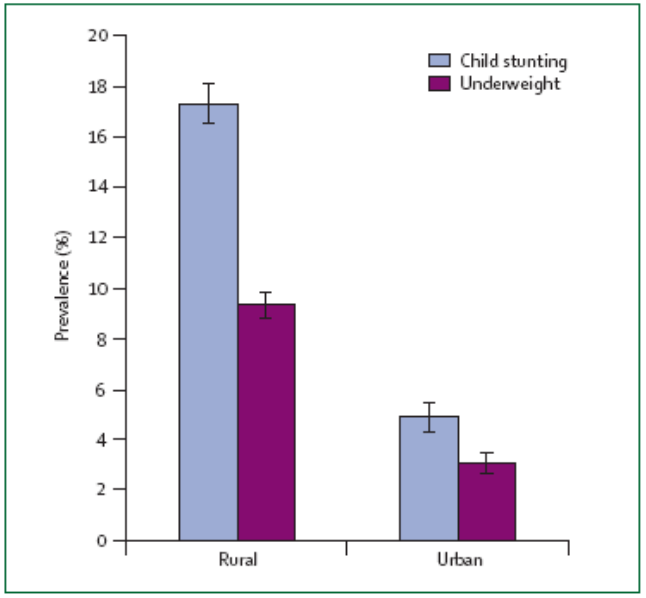


Figure 2: **Disparities in child malnutrition between urban and rural area of China 2002[11]**

Data are prevalence with 95% CI.

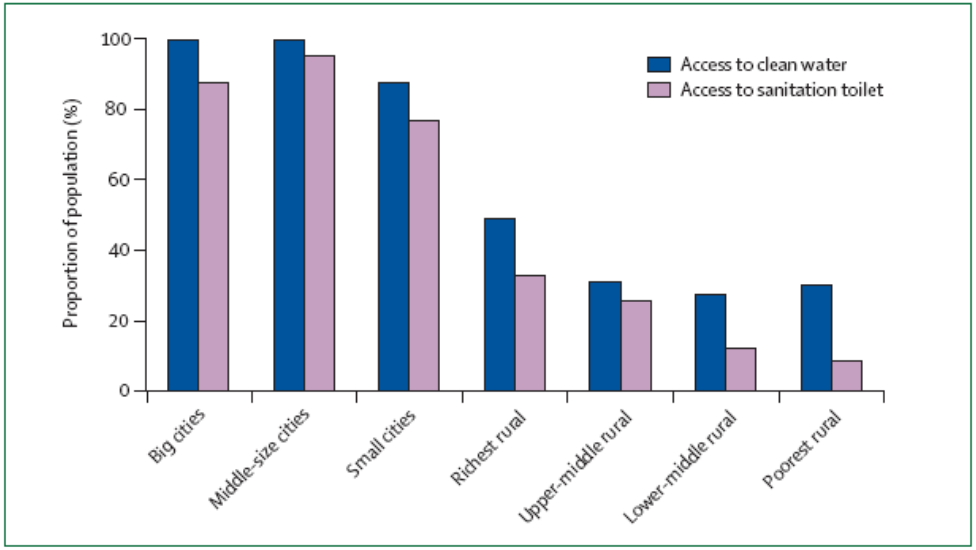
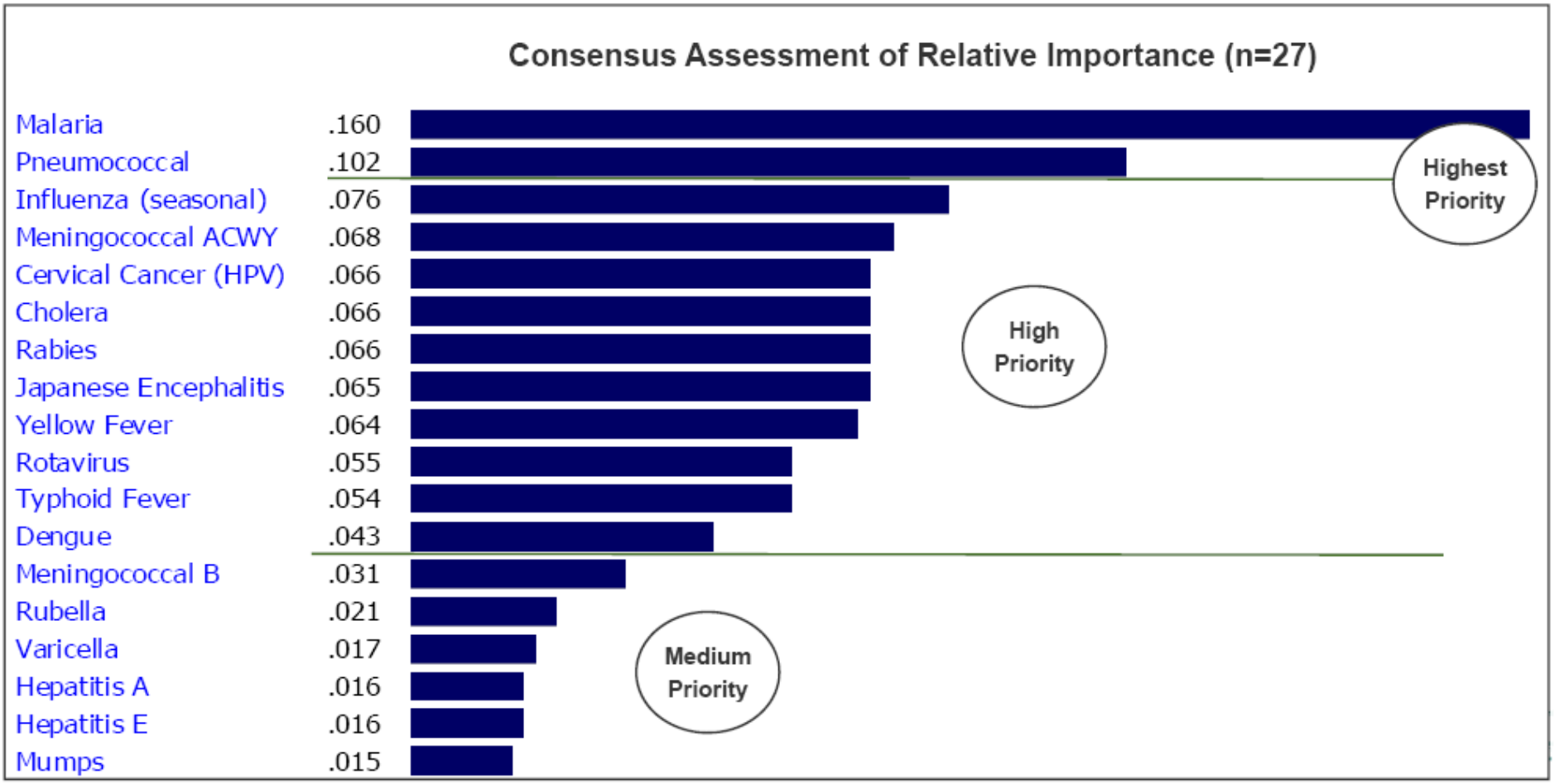


Figure 6: **Percentage of population with access to clean water and sanitation in different areas in 2003[47]**

Tang S et al Lancet 2008; 372:1493-1501

Vaccine Portfolio Development Process

FOUNDATION – WHO DISEASE PRIORITIZATION (Nov. 2007)

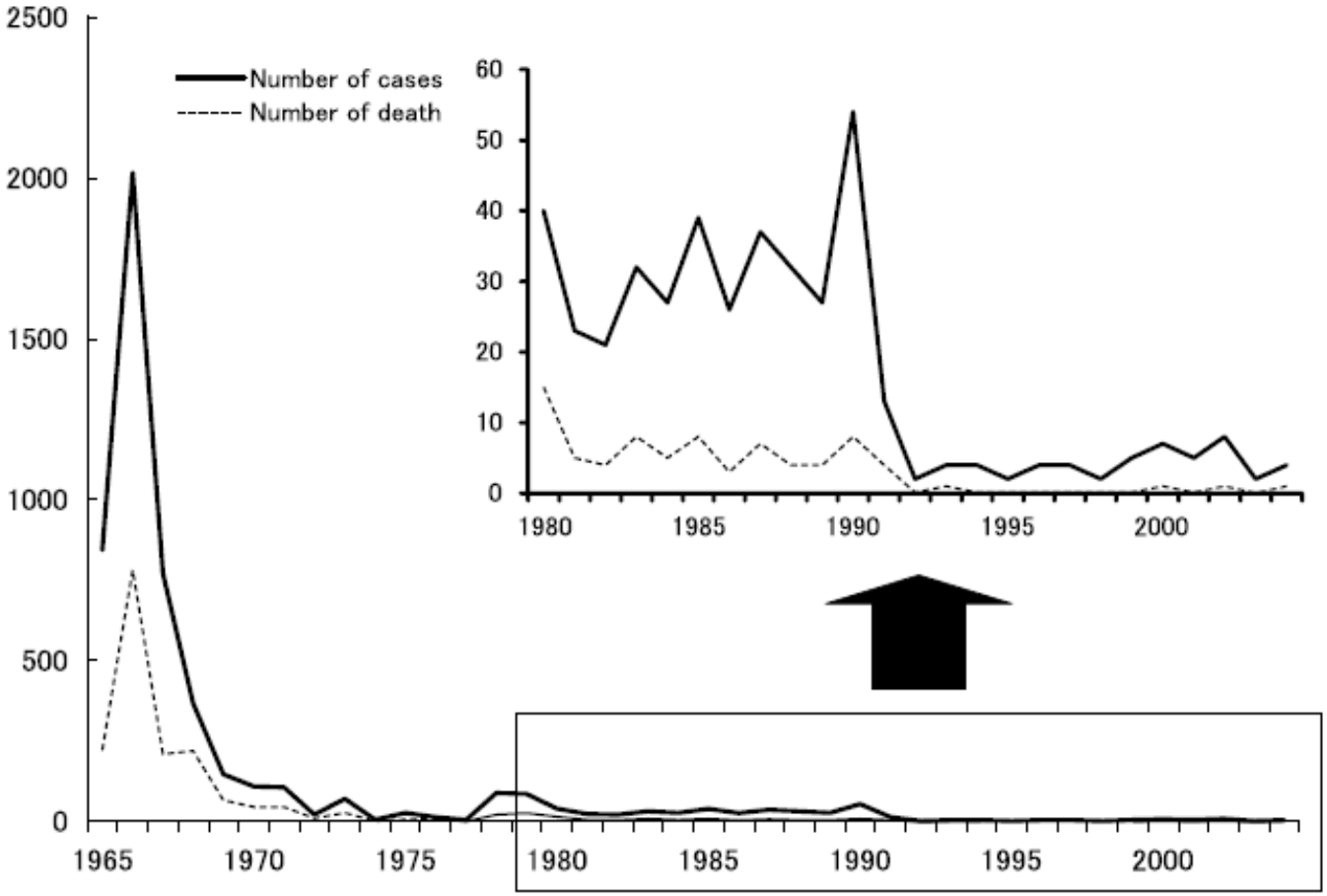


Qualifying criteria for tropical disease applications under section 524

Product for prevention or treatment of

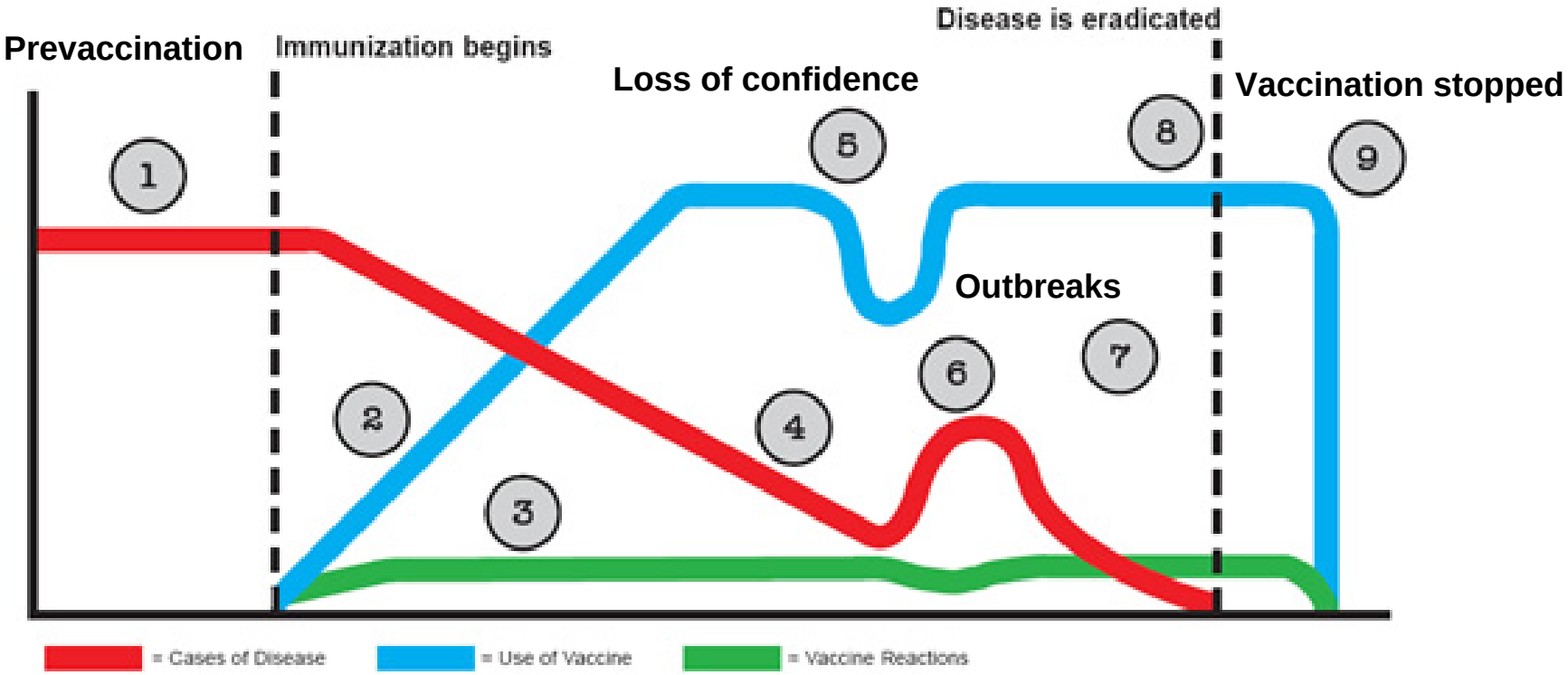
- Listed neglected tropical diseases
- Other infectious disease for which
  - There is no significant market in developed nations
  - That disproportionately affects poor and marginalized populations

Decline in Japanese encephalitis with introduction of routine childhood vaccination, Japan



Arai S et al. Japan J Infect Dis 2008;61:333-8

Life Cycle of an Immunization Program



adapted from:
Chen RT et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine 1994;12:542-50

Japan: In Last 30 Years, More Vaccines Have Been Removed from Recommendation than Added

- Japanese encephalitis
  - **Introduced - 1956**
  - **Acute Disseminated EncephaloMyelitis cases – vaccination made voluntary, 2005**
- MMR
  - **Introduced -1989**
  - **Aseptic meningitis cases – vaccine withdrawn 1993**
  - **MR reintroduced – 2005**
- Influenza (school age children)
  - **Introduced - 1976**
  - **Vaccine associated illness - 1979, low disease incidence**
  - **Made voluntary, 1994**
- DTwP
  - **Neurological deaths – recommendations suspended, 1975**
  - **Reinstated, 1975**

Japanese encephalitis vaccine demand in U.S. is limited

Vaccine doses distributed, as reported to CDC Biologicals Surveillance						
Vaccine	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
MPSV4	**1,296,864**	**1,424,442**	**1,414,499**	**1,768,664**	**1,512,084**	**677,060**
MCV4	**0**	**0**	**0**	**0**	**0**	**3,108,168**
PCV7	**13,663,100**	**15,256,865**	**11,314,990**	**15,076,530**	**15,624,972**	**17,365,055**
JE	**139,708**	**104,643**	**132,643**	**109,574**	**105,971**	**108,487**
Rabies	**155,822**	**200,752**	**189,330**	**185,447**	**273,341**	**-33**

- JE vaccine is distributed principally to the military
- No JE vaccine is licensed in Europe
  - Available for compassionate use – few doses distributed

Biologicals Surveillance, CDC

Qualifying criteria for tropical disease applications under section 524 – Japanese encephalitis

Product for prevention or treatment of

- Other infectious disease for which
  - There is no significant market in developed nations
    - Routine vaccine recommendation withdrawn in Japan
    - Travel/military vaccine demand – few doses used in U.S., Europe
  - That disproportionately affects poor and marginalized populations
    - Significant regional burden of disease
    - Affects 13 GAVI eligible countries and China
    - Disproportionately affects rural-dwelling children
    - Need prioritized by GAVI, WHO using systematic evaluation scheme – included among other diseases currently listed as section 524-qualified

Thank you!

NOVARTIS

Vaccine remains unavailable in the majority of countries where JE is endemic

- In 13 GAVI eligible countries –
  - **Limited vaccine distribution in Vietnam, Sri Lanka, Nepal, India**
  - **No systematic vaccination in Cambodia, Laos, Myanmar, Pakistan, Timor Leste, Indonesia, Papua New Guinea, Bangladesh, Bhutan**
- Insufficient volume of licensed vaccines for regional needs
  - **Available vaccines are distributed principally in countries of manufacture**
- Available vaccines have shortcomings
  - **Inactivated mouse brain – safety concerns, expense, BIKEN has discontinued production**
  - **Live attenuated SA_{14}-14-2 vaccine**
    - **Safety database poorly characterized**
    - **Unknown safety in HIV infected children**
    - **Unknown level/duration of viremia, potential for vectorborne transmission**
    - **Unknown impact of dengue immunity on vaccine take**

Principal Licensed JE vaccines

Date	Type	JE virus strain	Countries with widespread use
1930's	Inactivated mouse-brain derived vaccine e.g. (JE-VAX®)[1,2]	Nakayama or Beijing	Japan, Republic of Korea, Taiwan, and Thailand; some areas of Malaysia, Sri Lanka, and Viet Nam
1967	Inactivated, primary-hamster-kidney (PHK) cell-culture-derived vaccine (licensed in PR China[1,2])	Beijing P-3	China
1989	Live, attenuated, PHK cell-culture-derived vaccine (licensed in PR China[1,2])	SA 14-14-2	China (licensed for use in India, Nepal, Republic of Korea, and Sri Lanka)

1. GAVI alliance. Landscape analysis – Japanese Encephalitis. June 2008.
2. WHO Weekly Epidemiological Record, No.34/35, 25 August 2006.

IC51 Pediatric Development Plan

STUDIES PLANNED FOR INITIAL PEDIATRIC LICENSURE

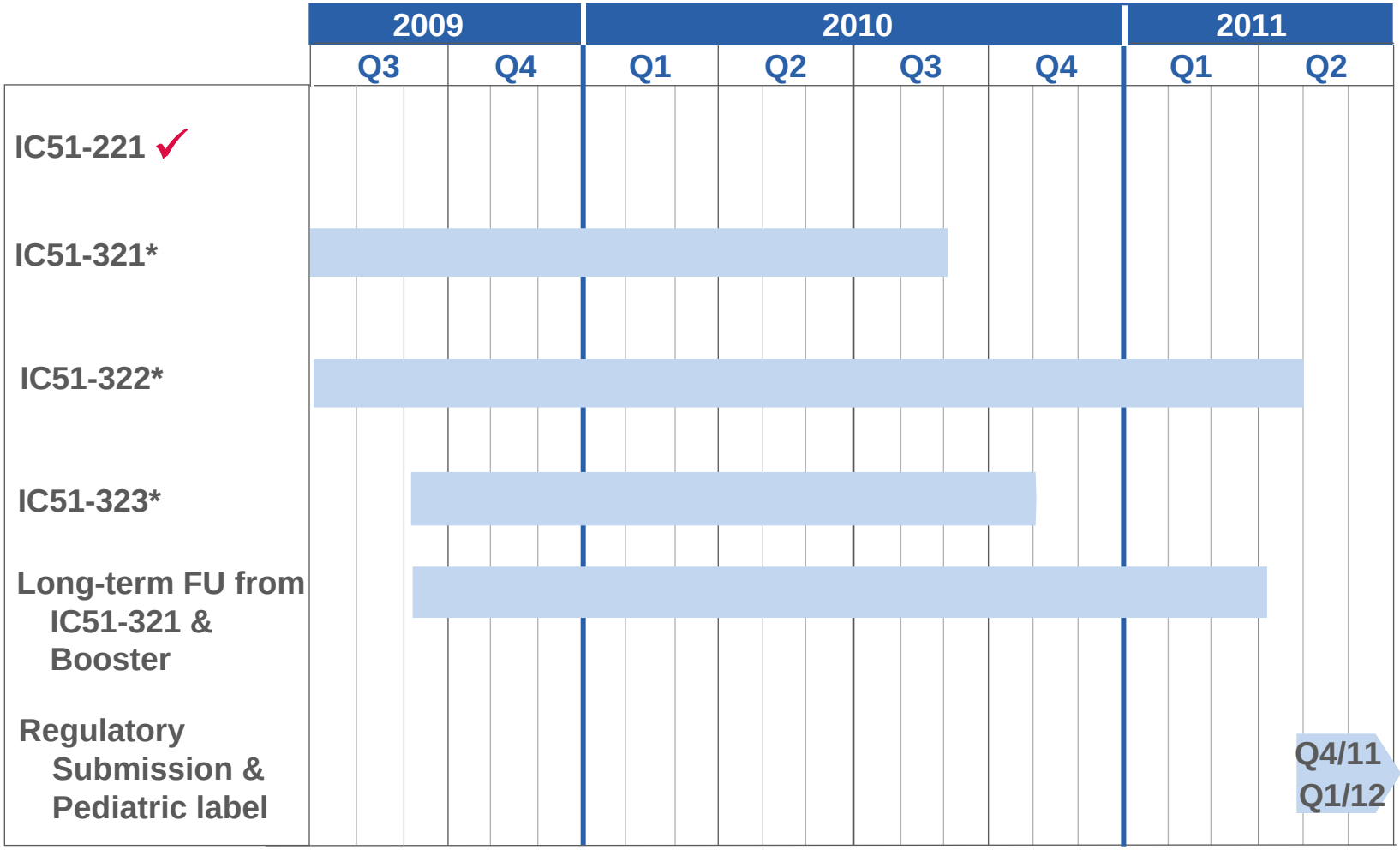
No/Phase	Dose	Age* (years)	N Total/ N IC51	Location	Objectives	Execution
IC51-221 Phase 2	2 x 6 µg, days 0, 28 2 x 3 µg, days 0, 28	≥ 1 to < 3	60/ 48	India	Safety, Immunogenicity and Dose confirmation	Biological E completed
IC51-321 Phase 3	2 x 6 µg**, days 0, 28	≥1 to < 3 ≥ 3 to < 18	468/234	SE-Asia	Immunogenicity and Safety compared to JenceVac	Start Q2/Q3 2009
IC51-322 Phase 3	2 x 6 µg**, days 0, 28	≥ 1 to < 3 ≥ 3 to < 18	50-100***	U.S./EU	Immunogenicity and Safety, non endemic	Start Q2/Q3 2009
IC51-323 Phase 3	2 x 6 µg**, days 0, 28	≥1 to < 3 ≥ 3 to < 18	1,150***	SE-Asia	Safety compared to active comparator	Start Q2/Q3 2009

* Lower age limit subject to confirmation

** 2 x 3 mcg < 3 years of age as of study IC51-221

*** Size of safety database awaits confirmation

Roadmap Pediatric Development



* Preliminary timelines, tbd after final agreement from regulatory authorities