The Clinical Epidemiology of Encephalitis

ESCMID Encephalitis Course
29-30 October 2014

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Head, Brain Infections Group

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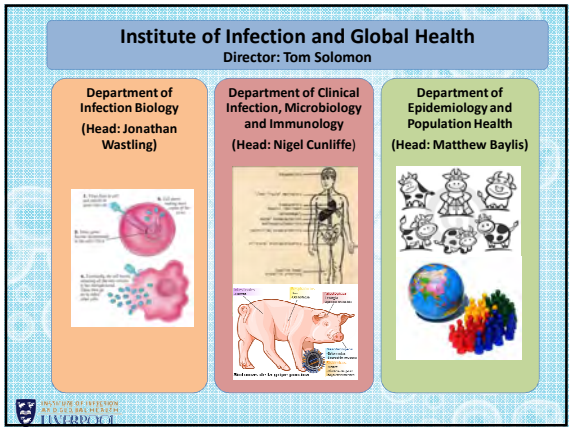
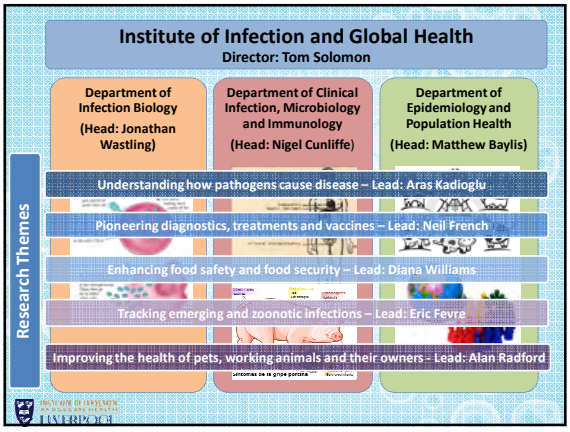
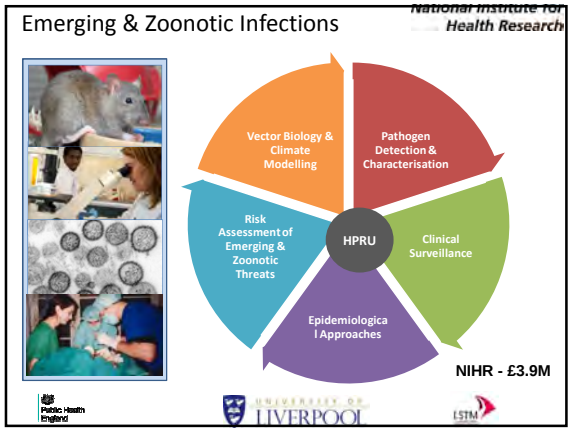
- Introduction
  - Brain Infections Group, Institute of Infection & Global Health, Liverpool
- Epidemiology
  - Basic concepts and Ideas
  - Changing epidemiology of encephalitis
- Some Examples
  - Europe
  - Global
  - Illustrative Cases
  - Our research, and others

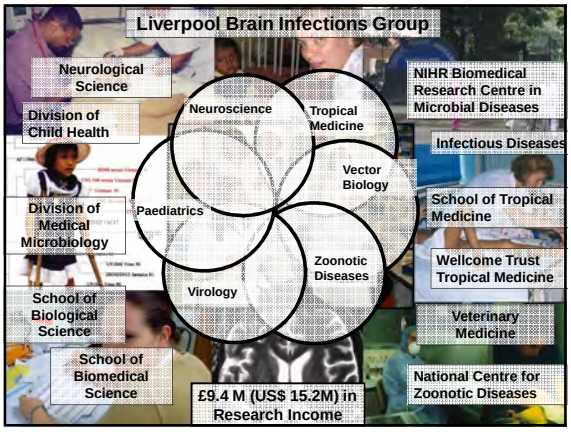






HPRU EBOLA WORK

c/o Julian Hiscox



Brain Infections Group Research Disciplines

Translation Research	Experimental Medicine	Applied / Programmatics
Pathogenesis	Clinical Research	Public Health
• Molecular Virology	• Clinical Epidemiology	• With WHO
• Inflammation	• Diagnostics	• Disease burden
• Histopathology	• Pathophysiology	• Education
• Disease models	• Case management	• Vaccine implementation
	• Treatment trials	

Research Areas

- HIV Brain Disease
- **Enterovirus 71,** Rabies
- **Jap Enceph**, Dengue, West Nile
- Dual CNS Infections
- **Herpes encephalitis**

Liverpool Brain Infections Group International Collaborations

- University of Oxford-Wellcome Trust Clinical Research Unit, Centre for Tropical Diseases, Ho Chi Minh City (since 1994)
- Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand (since 1994)
- Institute of Health and Community Medicine, Universiti Malaysia Sarawak, Malaysia (Since 1997)
- University of Texas Medical Branch, Galveston, Texas (since 2001)
- Queen Elizabeth Hospital, Blantyre, Malawi (since 2003)
- National Institute for Mental Health and Neurological Science (NIMHANS), Bangalore, India (since 2004)
- Centres for Disease Control Atlanta, and Colorado, Texas (since 2007)
- Kanti Children's Hospital, Kathmandu, Nepal (since 2009)
- Indian Institute for Science, Bangalore (2009)
- John Hopkins Baltimore, USA (2009)
- Washington University St Louis, USA (2009)
- Lerner Research Institute, Cleveland, Ohio (2010)

Epidemiology?

Epidemiology

- "the science that studies the patterns, causes, and effects of health and disease conditions in defined populations.
- It is the cornerstone of public health, and informs policy decisions and evidence-based practice by identifying risk factors for disease and targets for preventive healthcare."

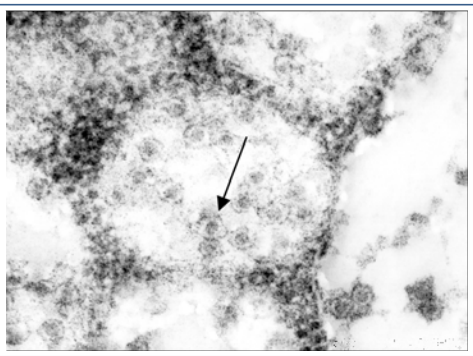
Clinical epidemiology

- The application of the science of epidemiology in a **clinical setting**. Emphasis is on a medically defined population, as opposed to statistically formulated disease trends derived from examination of larger population categories.

Epidemiology

- Who gets disease?
- How? Why? When? Where?
- Any impact of Disease control?
  - Vaccination? Other?
- Clinical epidemiology
- In addition:
  - how do they present, clinical features?
  - Diagnostics important, treatment?

Life as a virus



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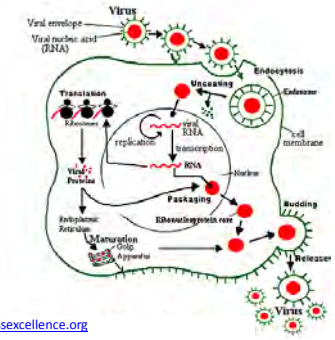
Virus replication (sex)



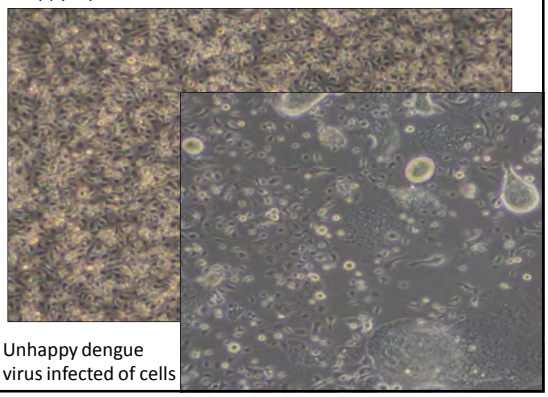
www.accessexcellence.org

Reproduction

10 genes

24,000 genes

Happy layer of cells

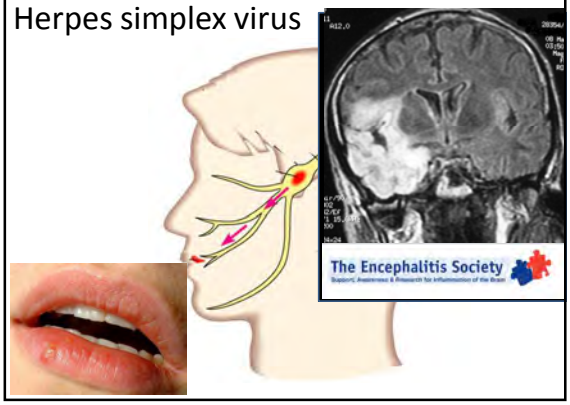


Unhappy dengue virus infected of cells

Viruses

Hiders and Jumpers

Herpes simplex virus



Brain Infections:

- How does pathogen get into the body?
- How does it get into the Central Nervous System?

Jumping Viruses

Routes of spread?

- Respiratory
- Gastrointestinal
- Mucosal
- Insect-borne
- Injections
- Congenital (mother to child)
- Sexually transmitted

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Respiratory

eofdreams.com

Gastrointestinal

www.motherandbaby.com.au/

Mucosal

funstuffcafe.com

Insect-borne

www.news.liv.ac.uk

Sexually Transmitted

Tropical Viral Infections

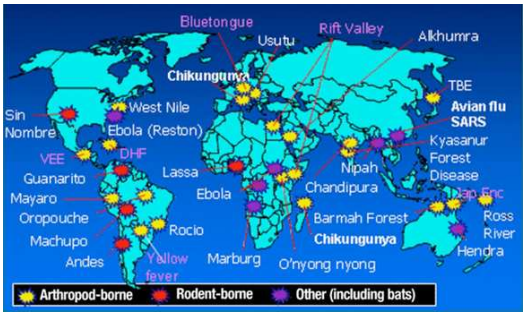
- Six questions to get a handle

- What is the Natural host?
  - Animals (zoonoses)
  - Humans
  - Unknown
- What is the habitat?
  - Urban
  - Rural
- How is it transmitted
  - Direct
  - Arthropod-borne (insects/ticks)
  - Both
- Where?
  - On Globe
- What disease syndrome?
  - Haemorrhagic (VHF)
  - FAR (fever arthralgia rash)
  - CNS
  - Other
- Is there nosocomial spread?

Definitions

- Pathogen
  - Bacteria, virus, parasite, causing disease
- Zoonotic Infections
  - Spread from animals to humans
- Arbovirus infections
  - Arthropod-borne viruses,
  - i.e transmitted by insects or ticks (arthopods)

Zoonoses - Infections that spread from animals to humans account for majority of emerging infections

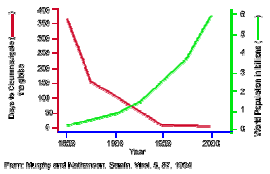


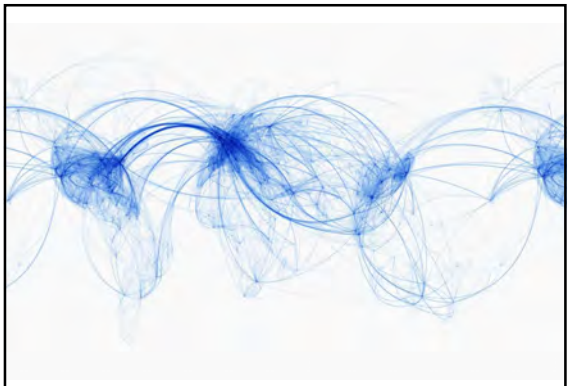
www.earthintransition.org/

Emerging diseases – why?

Emerging diseases – why?

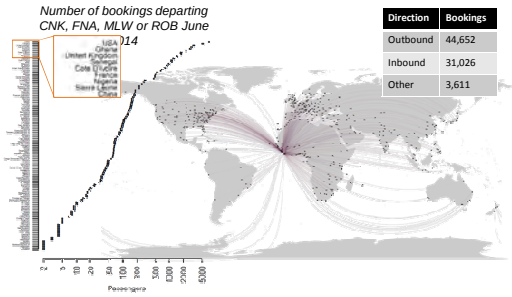
- Increasing & more rapid human travel
- Overpopulation
- Changing agricultural
- ?Global warming
- Better diagnostics
- Better reporting
- Greater awareness





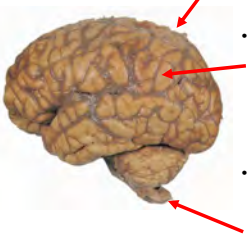
Airline Routes – No. Of airlines flying each route

Ebola risk: direct and indirect flights



USA at greatest risk of importing Ebola

Neuroanatomy



- Meningitis
  - *inflammation of meninges*
  - headache, vomiting, photophobia, neck stiffness, Kernig's signs. CSF pleocytosis
- Encephalitis
  - viral invasion/inflammation of brain parenchyma
  - behavioral change, 'psychiatric illness', confusion, coma, focal signs, convulsions
- Myelitis
  - *spinal cord (anterior horn cells)*
  - flaccid limb paralysis, absent reflexes

What are the key neuroscience questions?

- How does the pathogen get into the CNS?
- How does the pathogen damage neurones?
  - can we do something to stop it?
- How much does the host response contribute damage?
  - can we do something to stop it?

How does the pathogen get into the CNS?

How does the pathogen get into the CNS Two paradigms

Tracking up a nerve

- Herpes simplex virus
- Rabies virus

Viraemia and spread across the BBB

- Japanese encephalitis virus
- Enterovirus 71

Viral causes of encephalitis

Groups	Viruses
Herpes viruses (family Herpesviridae)	
	Herpes simplex virus type 1
	Herpes simplex virus type 2
	Varicella zoster virus type 1
	Epstein-Barr virus
	Cytomegalovirus
	Human herpes virus 6 & 7
Enteroviruses (Family Picornaviridae)	
	Enterovirus 70
	Enterovirus 71
	Poliovirus
	Coxsackieviruses, Echoviruses, Parechovirus
Paramyxoviruses (family Paramyxoviridae)	
	Measles virus
	Mumps virus
Others (rarer causes)	
	Influenza viruses, Adenovirus, Parvovirus B19, Lymphocytic choreomeningitis virus, Rubella virus,
Zoonotic viruses	
	Rabies, other lyssaviruses
	Nipah virus
Arboviruses (most are also zoonotic)	
Flaviviruses (family Flaviviridae)	
	West Nile virus
	Japanese encephalitis virus
	Tick-borne encephalitis
	Dengue
Alphaviruses (Family Togaviridae)	
	Western, Eastern and Venezuelan Equine encephalitis virus
	Chikungunya
Bunyaviruses	
	Lacrosse virus
Coltiviruses	
	Colorado tick fever
Vesiculoviruses	
	Chandipura virus

Non-Viral causes of encephalitis and encephalopathy

CNS infections

Bacteria

Small bacteria (mostly intracellular)
- Mycoplasma
- Chlamydia
- Rickettsia (including scrub typhus, rocky mountain spotted fever)
- Ehrlichiosis
- Coxiella (Q fever)
- Bartonella (Cat Scratch fever)
- *Tropheremа whippleі* (Whipple's disease)
- Brucellosis
- Typhoid fever

Spirochetes
- Syphilis
- Lyme Neuroborreliosis
- Leptospirosis
- Borrelia recurrentis (Relapsing fever)

Other bacteria
- Subacute bacterial endocarditis
- Listeria
- Nocardia
- Actinomycosis
- Parameningeal infection
- Abscess

Parasites
- Malaria
- Trypanosomiasis
- Amoebic encephalitis - *Naegleria fowleri*
- Cysticercosis
- Echinococcus
- Trichinosis
- Amoebiasis

Fungi
- Cryptococcus
- Candidiasis
- Coccidiomycosis
- Histoplasmosis
- North American blastomycosis

Para/Post infectious causes
- Acute disseminated encephalomyelitis
- Viral illnesses with febrile convulsions
- Shigella
- Viral infections associated with swollen fontanelle
- Guillain-Barré syndrome

Non infectious diseases

Vascular
- Vasculitis
- Systemic lupus erythematosis
- Behcet's disease
- Sub-arachnoid & sub-dural haemorrhage
- Ischaemic cerebrovascular accidents

Neoplastic
- Primary brain tumour
- Metastases
- Paraneoplastic limbic encephalitis

Metabolic encephalopathy
- Hepatic encephalopathy
- Renal encephalopathy
- Hypoglycaemia
- Reye's syndrome
- Toxic encephalopathy (alcohol, drugs)
- Hashimoto's disease

Other
- Drug reactions
- Epilepsy
- Hysteria
- Voltage gated K channel limbic encephalitis

Epidemiology of encephalitis

Epidemiology

- Some pathogens constant across globe,
  - e.g. HSV
- Others varies with geography
  - Esp Arthropod-borne & Zoonotic
- HIV and other immunocompromise has changed epidemiology
  - CMV, EBV, Toxoplasma more important
- Vaccination has changed epidemiology in some places
  - Polio, Measles, Mumps, Japanese encephalitis

Arboviruses – growing in importance

- West Nile virus in USA and Europe
- Tick-borne encephalitis virus in Europe
- Dengue and Chikungunya spreading

- Impact of
  - climate change?
  - Changing agricultural practice
  - People movement
  - etc

Encephalitis Incidence


Virology Journal

Review

Open Access

The incidence of acute encephalitis syndrome in Western industrialised and tropical countries

Fidan Jmor[1], Hedley CA Emsley[1], Marc Fischer[3], Tom Solomon[1,2] and Penny Lewthwaite*[1]

- 12,000 articles screened → 87 papers reviewed → 25 examined incidence of encephalitis

Jmor et al 2008

Incidence of Acute Encephalitis Syndrome (AES)

- Case definitions and diagnostic criteria, aetiologies, study types and reliability varied
- Incidence varies with geography, and age
- Western industrialised settings, incidences of AES
  - 10.5–13.8 per 100,000 for children
  - 2.2 per 100,000 for adults
- All age groups, incidences of AES
  - 6.34 per 100,000 tropical settings
  - 7.4 per 100,000 Western setting.

Jmor et al 2008

A man that was sleepy

t

Mr KR, Hx, Exam

- 52 male, 1 week Hx of
- Fever, frontal headache, malaise, lethargic, Sleeping ++ 15 hrs/day
- Occ blurring of vision
- Poor coordination
- Hiccoughs 24hrs
- No photophobia, No neck stiffness
- Mild dry cough, watery diarrhoea, itching after hot bath
- 2/12 earlier Scuba Diving in Egypt
- PMHx Hep A 1996

- O/E
- Pyrexial 38.5, NIL else
- CXR normal
- Na 127

Thoughts & next steps?

t

What would you do next?

- CT
- Start antibiotics
- LP
- Observe
- Malaria film

t

Differential, Progress

- **Day 1 DD** ?SBE, infective, tropical, ?underlying malignancy
- **Day 2, SHO**
- DD ?Atypical pneumonia
  - (chest clear, sats 99%)
- BCs, malaria film, Rx clarithromycin
- Haloperidol for hiccoughs
- **Day 3**
- Temp Up, Periph WCC up
- **Day 5**
- Still headache, temp 40, voice sl slurred, v sleepy (haloperidol)
- CT head

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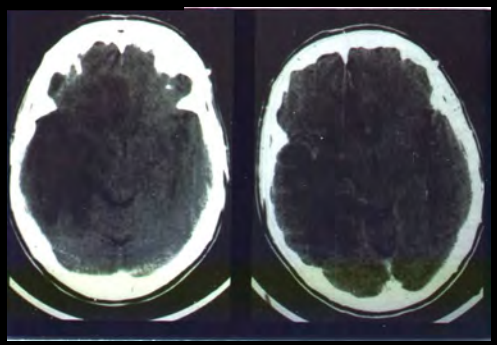
Similar to this



Report: Could be infective in nature;

- Day 5, 19.00pm LP done
- Day 6, 10.30am, results
  - WCC 220 (lymphocytes),
  - RCC<4, Protein 1.75, Gluc 2.5
- Orientated in T, S & P
- Await AFB, d/w neurosurgery
- D7 Repeat bloods
- D8, insuff CSF for TB/AFB

Neurologist called: Imp Meningitis / Encephalitis
Rx IV Aciclovir, await MRI brain
CSF positive by PCR for HSV type 1

t

The basics

- Encephalopathy – definition
  - Syndrome of Altered consciousness
  - Many cases included infections, metabolic, etc
- Encephalitis – definition
  - Strictly pathological diagnosis, inflammation brain parenchyma
  - Surrogate markers used
  - Causes
    - Viral, small intracellular bacteria, parasites immune mediated

t

Learning Points from this case

- Presentation can be subtle, fluctuant
- Clues
  - Lethargy Drowsiness, Sleeping 15hrs/day, Severe Headache, Hiccoughs, SIADH
- Beware “atypical pneumonia”
- Chase and act on LP result

→r

HSV encephalitis annual incidence

- Most studies 2-4 per million, annually
  - 1-2 per 250,000, annually
  - Each DGH (300,000) 2-3 cases per year
- USA (Johnstone 1998)
  - 2000 annually (population 291 million)
  - 6.9 per million annually
- UK Hospital Statistics (Davison et al EID 2003)
  - 120-175 cases annually (1989-98) (population 60 million)
  - 2-3 per million

Incidence – Any Viral Encephalitis

- Most studies: 5-10 per 100,000
  - Expect 3000-6000 annually in UK
- Average DGH (300,000)
  - 15-30 cases per year
  - 1-2 viral encephalitis per month
- UK Hospital Episode Statistics
  - 6400 cases of suspected encephalitis in 10 years
  - 1.5 per 100,000 (under-reporting)
  - 3800 unspecified
  - 1400 HSV
  - 300 VZV
  - 64 “exotic”
  - (measles mumps, rubella, adenovirus, LCMV)

Beghi 1984
Davison et al EID 2003

HSV encephalitis

- Most is HSV type 1
  - Oral transmission
- About 10% HSV type 2
  - Genital transmission
  - (more often causes meningitis)
  - Causes encephalitis in immunocompromised adults, and neonates
  - In children → consider for sexual abuse

What are the clinical features of encephalitis?

- Classically
  - Flu-like prodrome, rapidly followed by severe headache, nausea, vomiting, altered consciousness, seizures, focal signs, meningism
- Subtle presentations
  - Low grade fever, behavioural changes, speech and language disturbances
  - Especially in immunocompromised

Why encephalitis is missed

- Wrongly attributing a patient's **fever and confusion**
  - "urinary tract infection"
  - "chest infection"
- Failure to **recognise a febrile illness**,
  - "afebrile on admission"
- **Ignoring a relative** says patient behaviour, "not quite right"
  - "Glasgow coma score =15"
- Wrongly attributing clouding of consciousness
  - **"drugs or alcohol"**
- Failure to properly investigate a patient with a fever and **seizure**

- **Failure to do a lumbar puncture, even though there are no contraindications**

New UK guidelines on encephalitis

Journal of Infection (2012) 64, 449–477

ELSEVIER

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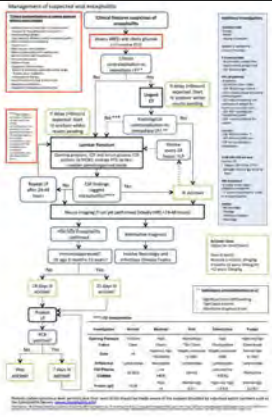
www.elsevierhealth.com/journals/jinf

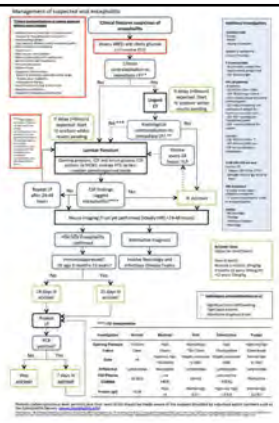
Management of suspected viral encephalitis in children – Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guidelines

R. Kneen [a,b,r,*], B.D. Michael [b,c,i,j,r], E. Menson [d,k], B. Mehta [a,l], A. Easton [e,m], C. Hemingway [f,n], P.E. Klapper [g,o], A. Vincent [h,p], M. Lim [d,k], E. Carrol [a,q], T. Solomon [b,c,i,j], On behalf of the National Encephalitis Guidelines Development and Stakeholder Groups

Management Alogrithm



Management Alogrithm



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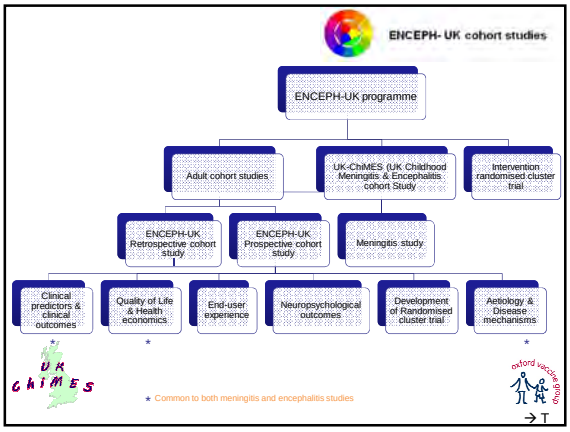
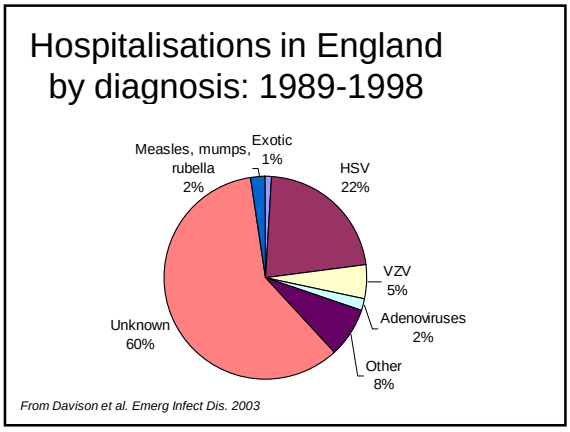
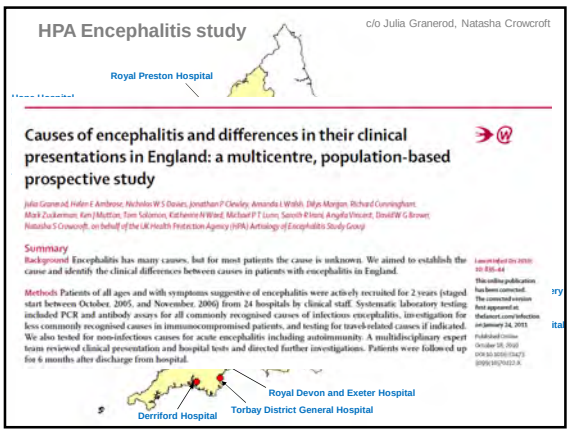
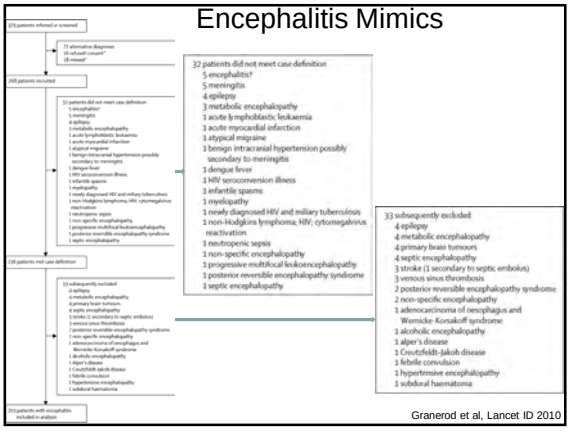
Understanding and Improving the Outcome in Encephalitis

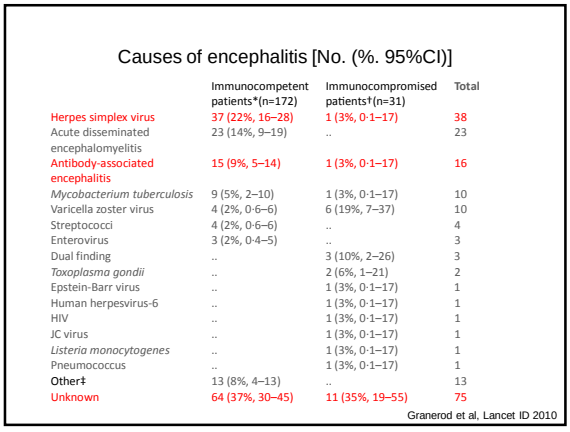
National Institutes for Health Service Research (NIHR) Programme Grant











Causes of encephalitis [No. (%. 95%CI)]

	Immunocompetent patients*(n=172)	Immunocompromised patients†(n=31)	Total
Herpes simplex virus	37 (22%, 16–28)	1 (3%, 0·1–17)	38
Acute disseminated encephalomyelitis	23 (14%, 9–19)	..	23
Antibody-associated encephalitis	15 (9%, 5–14)	1 (3%, 0·1–17)	16
Mycobacterium tuberculosis	9 (5%, 2–10)	1 (3%, 0·1–17)	10
Varicella zoster virus	4 (2%, 0·6–6)	6 (19%, 7–37)	10
Streptococci	4 (2%, 0·6–6)	..	4
Enterovirus	3 (2%, 0·4–5)	..	3
Dual finding	..	3 (10%, 2–26)	3
Toxoplasma gondii	..	2 (6%, 1–21)	2
Epstein-Barr virus	..	1 (3%, 0·1–17)	1
Human herpesvirus-6	..	1 (3%, 0·1–17)	1
HIV	..	1 (3%, 0·1–17)	1
JC virus	..	1 (3%, 0·1–17)	1
Listeria monocytogenes	..	1 (3%, 0·1–17)	1
Pneumococcus	..	1 (3%, 0·1–17)	1
Other‡	13 (8%, 4–13)	..	13
Unknown	64 (37%, 30–45)	11 (35%, 19–55)	75

Granerod et al, Lancet ID 2010

What are the clinical features of encephalitis?

Clinical features [No. (%), 95%CI)] of encephalitis in HPA study

	All encephalitis* (n=203)	HSV (n=38)
Fever	147 (72, 66–78)	29 (76, 60–89)
Headache	122 (60, 53–67)	16 (42, 26–59)
Seizures	105 (52, 45–59)	24 (63, 46–78)
Lethargy	111 (55, 48–62)	16 (42, 26–59)
Irritability	75 (37, 30–44)	11 (29, 15–46)
Personality/behavioural change	131 (64, 57–71)	24 (63, 46–78)
Stiff neck	46 (23, 17–29)	5 (13, 4–28)
Focal neurology	73 (36, 29–43)	16 (42, 26–59)
Coma (GCS</=8)	37 (18, 13–24)	9 (24, 11–40)
Neurological signs**	61 (30, 24–37)	9 (24, 11–40)
Gastrointestinal symptoms**††	98 (48, 41–55)	13 (34, 20–51)
Respiratory symptoms**††	41 (20, 15–26)	5 (13, 4–28)
Rash**	23 (11, 7–16)	2 (5, 0·6–18)
Photophobia**	16 (8, 5–12)	3 (8, 2–21)
Urinary symptoms**††	21 (10, 6–15)	1 (3, 0·1–14)

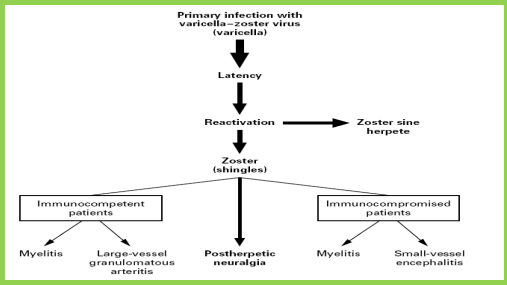
→R

Granerod et al, Lancet ID 2010

Varicella encephalitis

- Rare
- Vasculitis involved in pathology
- No evidence but treatment usually with aciclovir & steroids
- Varicella may also cause other neurological presentations including para/post infectious cerebellitis, myelitis, stroke

Neurologic Complications of the Reactivation of Varicella–Zoster Virus



Gilden et al NEJM 2000

Another Case

Little Linh

History

- Linh , 4-year-old in Southern Vietnam
- Four-day illness.
- 2 days High fever, runny nose, cough, and sore throat.
- No vomiting or diarrhoea.
- Day 3 mother bought a mixture of unknown drugs at a local store - did not lower the fever.
- Day 4 Confused, her eyes rolled up, and she had intermittent twitching and spasms in her face.

- Linh is fourth of 4 children
- Vaccinated against measles and polio.
- No previous major illnesses
- No family history of note.
- Lived with her parents, siblings and grandparents in a poor area on the edge of Ho Chi Minh city.
- Father was a cyclo-driver.

Examination

- Tmperature was 39°C, pulse 132, respiratory rate 40, blood pressure 110/80.
- No rash or lymphadenopathy;
- heart sounds were normal,
- Bilateral coarse crackles in the chest
- Abdominal examination was normal.

- Neuro Exam - Signs?
- Unconscious
- - an abnormal flexion response to pain,
- - no eye movements,
- - no verbal response to pain.

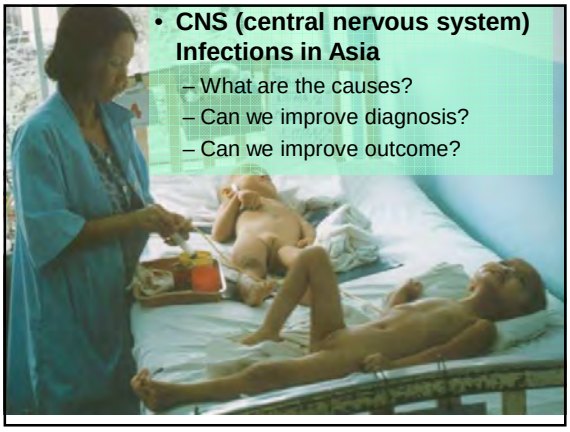
- Continuous twitching - left side of face.
- No neck stiffness.
- Limbs were flaccid with absent deep tendon reflexes in the legs

Differential diagnosis

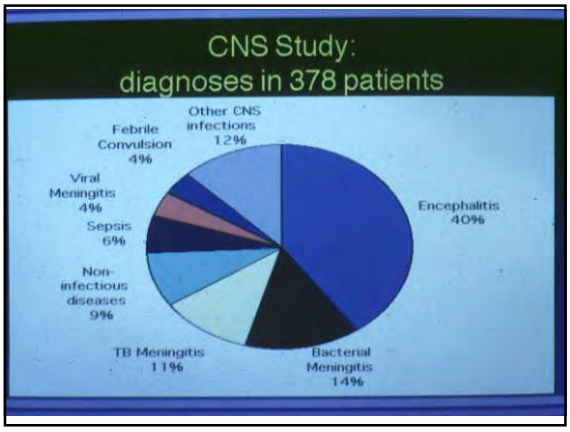
Differential diagnosis

- Arboviral encephalomyelitis
- Japanese encephalitis, other
- Other viral encephalitis
- Herpes Simplex Virus 1, Herpes Zoster Virus, Enteroviruses
- Polio, Rabies
- Acute Disseminated encephalomyelitis
- Post infectious – measles
- Post vaccine
- Bacterial Meningitis/Abscess
- TBM
- Cerebral Malaria
- Tetanus
- Drugs/Toxins
- Secondary Bacterial Pneumonia

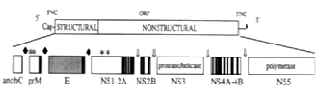
Qn 2 List the investigations you would do?



- **CNS (central nervous system) Infections in Asia**
  - What are the causes?
  - Can we improve diagnosis?
  - Can we improve outcome?

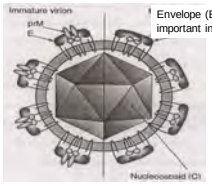


Japanese encephalitis virus (JEV)

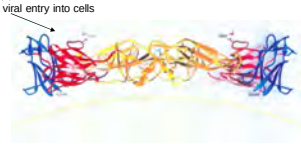


- *Flavivirus, Flaviviridae*
- West Nile virus
- Dengue

4 genotypes of JEV recognised



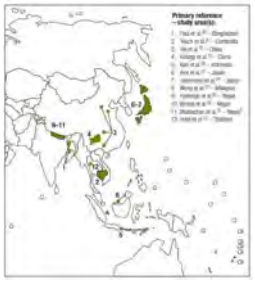
Envelope (E) protein important in viral entry into cells



Rey et al, Nature 1994

Estimated global incidence of Japanese encephalitis: a systematic review

Grant L Campbell,[a] Susan L Hills,[b] Marc Fischer,[b] Julie A Jacobson,[c] Charles H Hoke,[d] Joachim M Hombach,[e] Anthony A Marfin,[f] Tom Solomon,[g] Theodore F Tsai,[e] Vivien D Tsu[f] & Amy S Ginsburg[f]



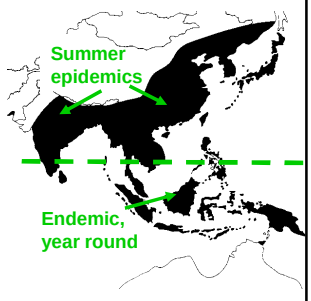
- Thirty-two areas endemic for JE in 24 Asian and Western Pacific countries sorted into 10 incidence groups
- Approx 67 900 JE cases typically occur annually
  - 1.8 per 100 000
  - **5.4 per 100 000 in children**

Bull World Health Organ 2011;89:766–774E

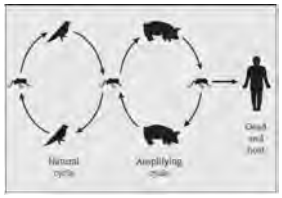
Japanese encephalitis (JE)

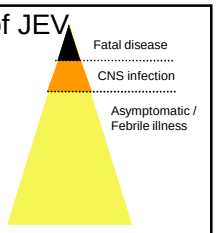
- 70,000 cases/year
- 10-30% mortality

- Vaccines
  - Expensive
  - Not available to most
- No antiviral treatment



Natural History of JEV

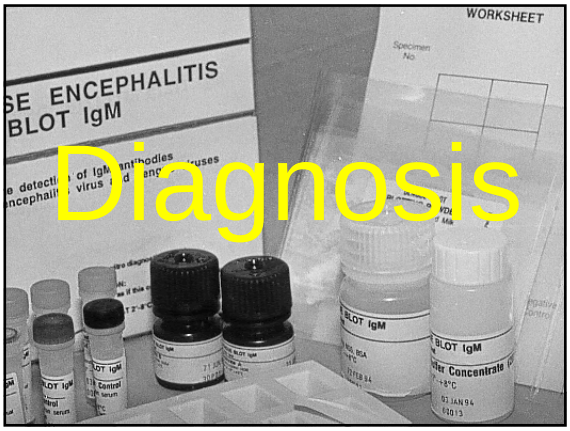




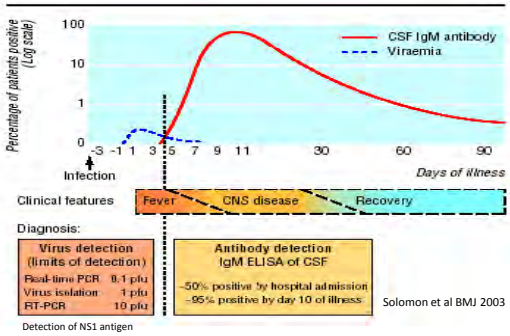
- Mosquito vectors – *Culex tritaeniorhynchus* and others
- Apparent to inapparent infection:
  - 1 in 25 (service personnel),
  - 1 in 300-1000 (children)

Japanese encephalitis: Epidemiology

- Cycle
  - Birds->pigs->humans
- Vector
  - *Culex tritaeniorhynchus*
- Rural/Peri-urban
- Virus ubiquitous
- 1 in 300 infections symptomatic
- SE Asia, India, Western Pacific, China
  - Summer epidemics in temperate North
  - Endemic/sporadic in tropical South
- Expanding
- 40-60,000 cases/year
- children>adults in Asia
- Non immune adults susceptible



Diagnostic arbovirology



Solomon et al BMJ 2003

JE: Clinical features

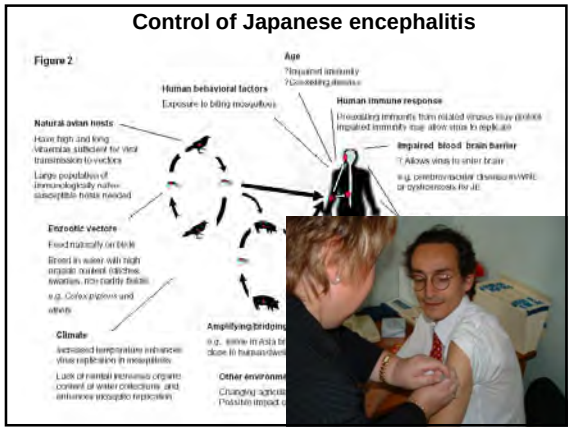
- Fever, headache, coma
- Convulsions*
  - ?subtle motor Sz
- Raised ICP*
- Polio-like flaccid paralysis
- 'Parkinsonism'
  - mask-like facies
  - cogwheel rigidity
  - tremor
- Outcome
  - 20% fatal,
  - 40% sequalae
  - 30% recovery
- Complications *
  - pneumonia
  - malnutrition
  - contractures
  - bedsores

* Management

Clinical features represent the anatomical location (Parkinsonism, flaccid paralysis); seizures and raised intracranial pressure may be treatable

Disease Control

Control of Japanese encephalitis



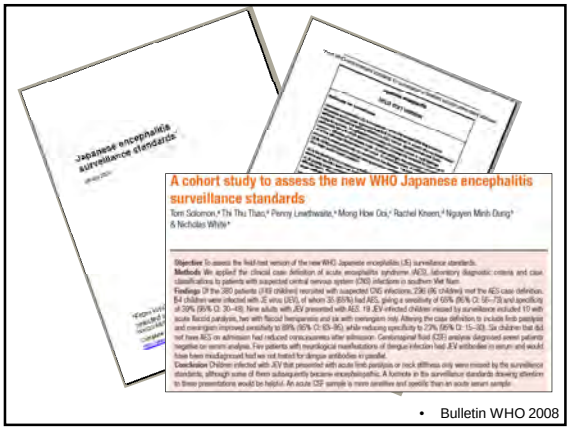
Vaccines against JE

	Virus strain	Name/Manufacture/Developer
Inactivated vaccines		
Mouse brain	Nakayama	Japan, BIKEN
Mouse brain	Nakayama	Korea, Green Cross
Mouse brain	Beijing-1	Japan
Primary hamster kidney	P3	China
Vero cell	P3/Beijing-1/ SA14-14-2/P3	China/Japan/US Army/ Aventis Pasteur
Live attenuated vaccines		
Primary hamster kidney	SA14-14-2	China
(Primary hamster kidney	SA14-5-3	China)
Recombinant vaccines		
(Canarypox vectored	Nakayama	NYVAC-JE, Japan/USA)
(Vaccinia vectored	Nakayama	ALVAC-JE, Japan/USA)
17-D yellow fever vectored	SA14-14-2	Chimerivax-JE, Acambis
DNA vaccine	Various	Various

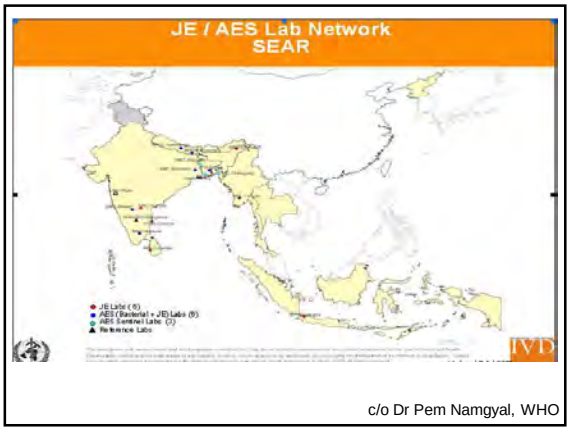
Solomon, T Control of Japanese encephalitis – within our grasp? NEJM 2006

Control of Japanese Encephalitis — Within Our Grasp?

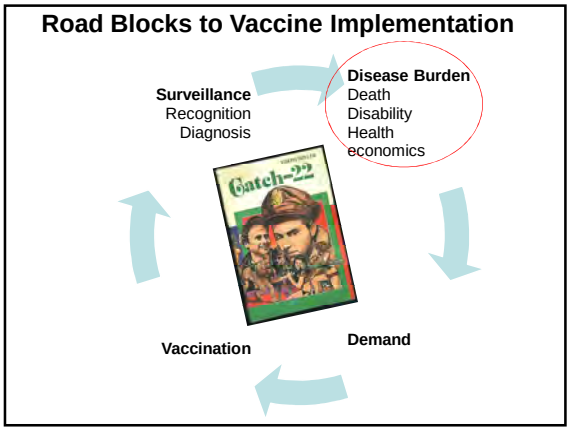
Tom Solomon, M.R.C.P., D.T.M.H., Ph.D.



- Bulletin WHO 2008



c/o Dr Pem Namgyal, WHO



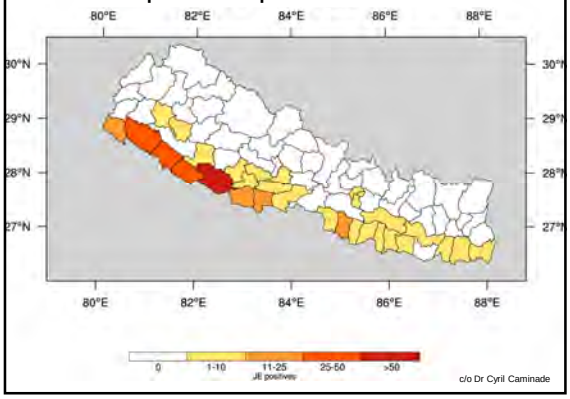
Japanese encephalitis Control Programme: 2005-2013

- Vaccination in in 11 new countries
- More than 200 million vaccinated
- Estimated 854,000 cases and 214,000 deaths avoided
- Associated saving US$ 1.024 billion across Asia

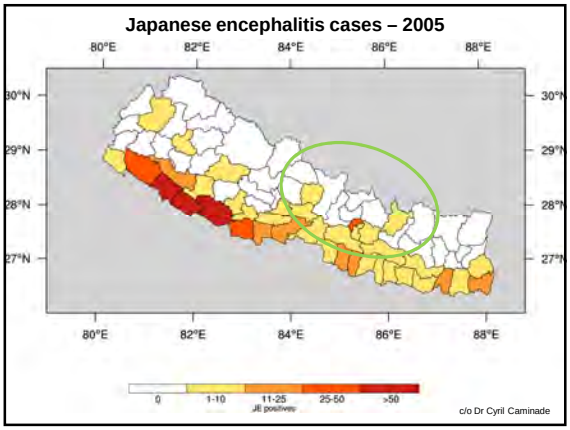
Japanese encephalitis is spreading - why?

Climate Change and Japanese encephalitis

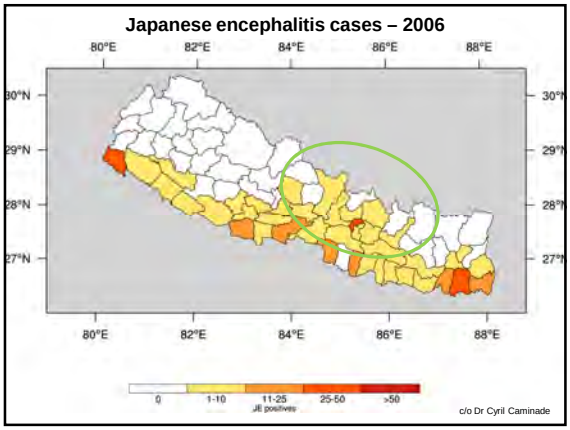
Japanese encephalitis cases – 2004



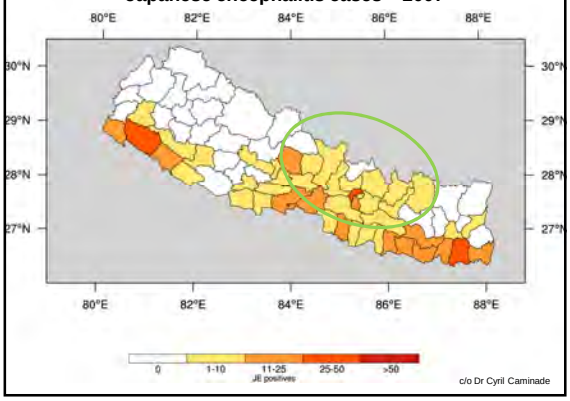
Japanese encephalitis cases – 2005

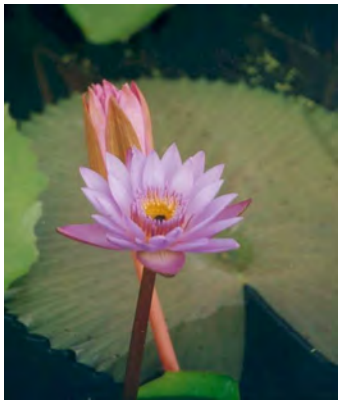


Japanese encephalitis cases – 2006

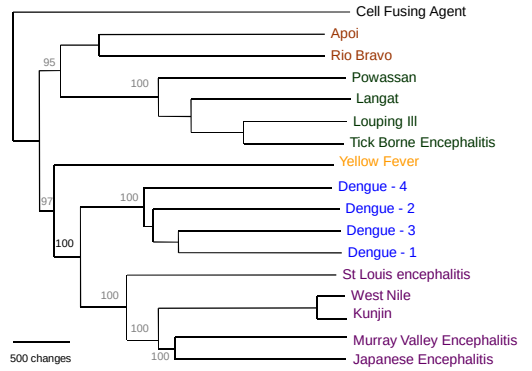


Japanese encephalitis cases – 2007

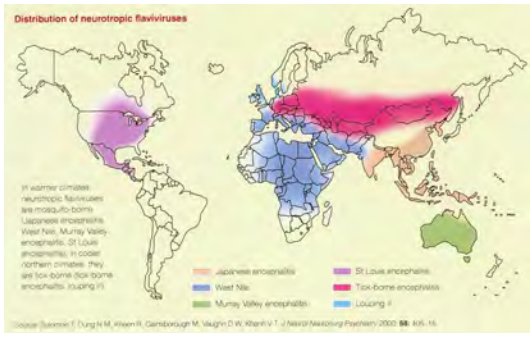


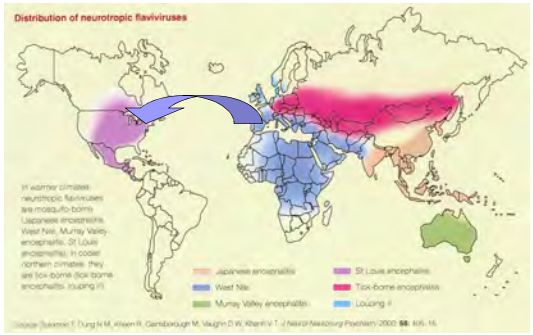


Maximum Parsimony Phylogeny of the Flaviviruses



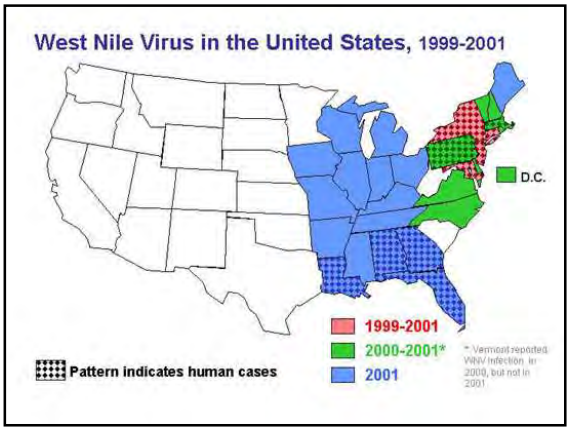
Solomon, J Neurovirol, 2003

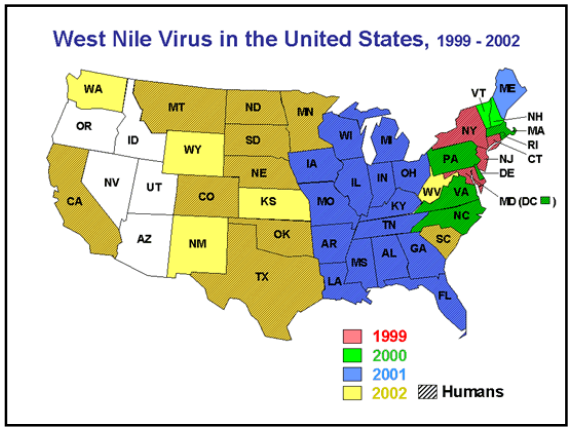


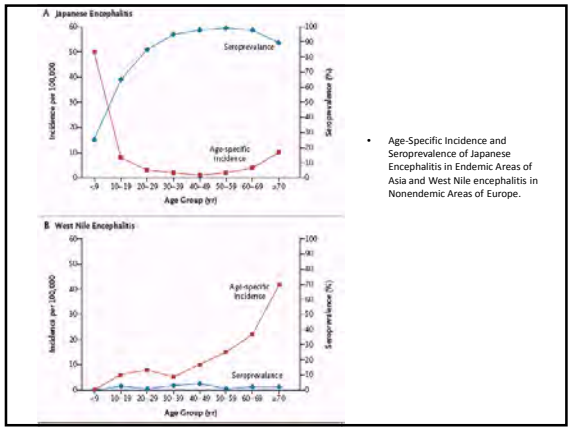


West Nile virus arrives in USA

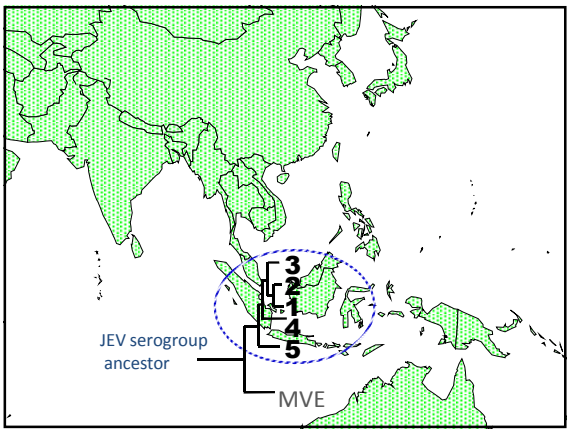
Welcome to Texas

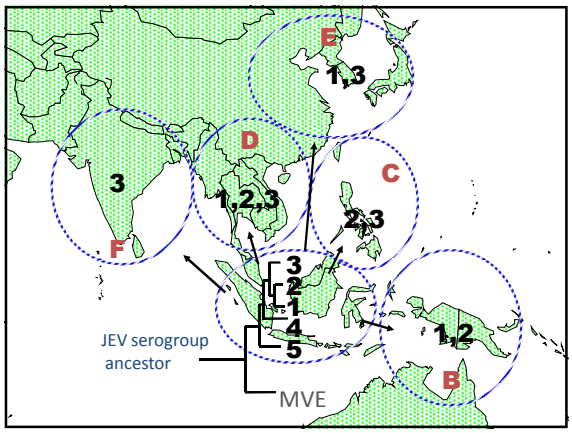


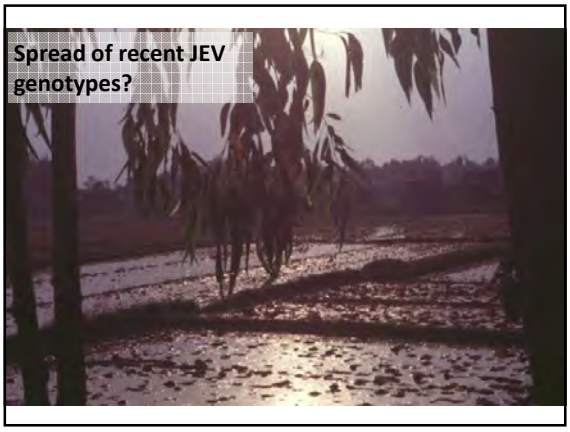


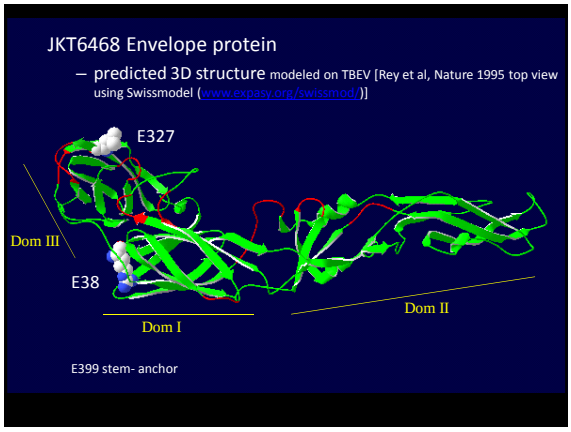


- Age-Specific Incidence and Seroprevalence of Japanese Encephalitis in Endemic Areas of Asia and West Nile encephalitis in Nonendemic Areas of Europe.

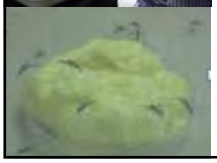








Transmission of Japanese encephalitis virus through mosquito vectors



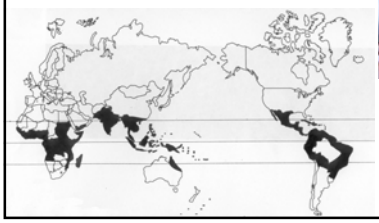
Daniel Impoinvil

- Does vector competence differ for different genotypes?
- How might climate change affect this?
- Can this inform modeling of disease spread?

- Leverhulme Foundation (£750,000)
  - Matthew Bayliss (Vet School, PI)
  - Mike Lehane (School of Tropical Medicine)

Dengue

- Mosquito-borne flavivirus
  - Dengue Fever / DHF
- 100 million cases per year



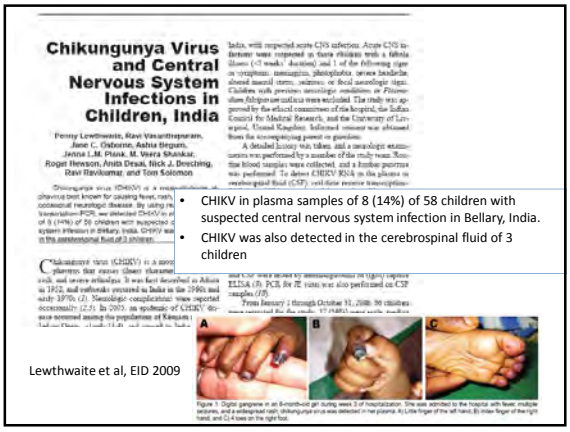
Neurological Manifestations of Dengue

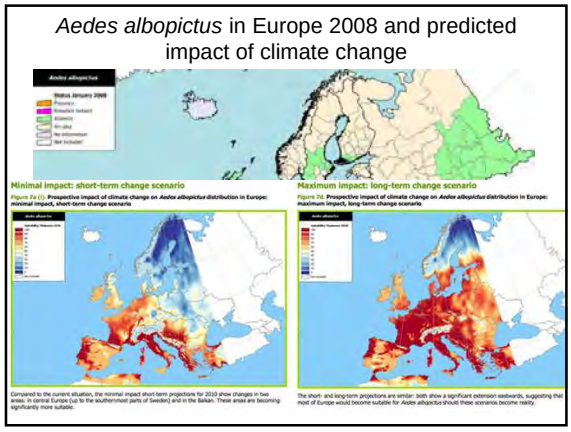
Solomon et al. Lancet 2000

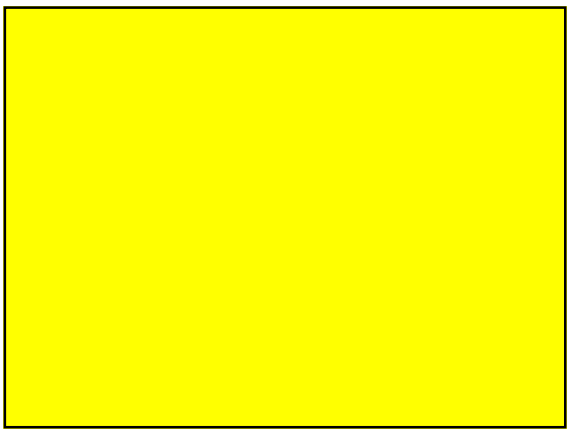
- 5% of suspected CNS infections
  - 6 (4.2%) of 378 CNS patients vs. 4 (1.4%) of 286 controls [OR 3.1 (1.7-5.8 p=0.039)]
- Pathophysiology
  - Encephalopathy as part of severe DHF
  - Dengue viruses cross blood brain barrier -> 'encephalitis'

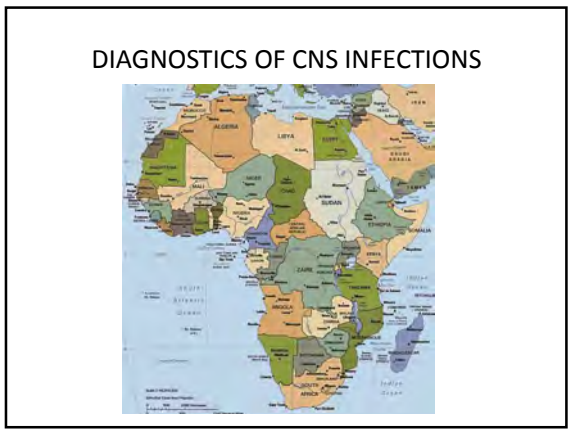
Similar incidence reported in Thailand, India (Chokephaibulkit, K, Paed ID 2002)

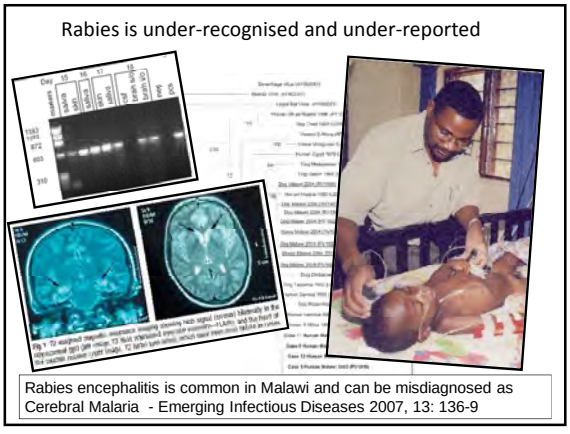
Model of flavivirus neurotropism

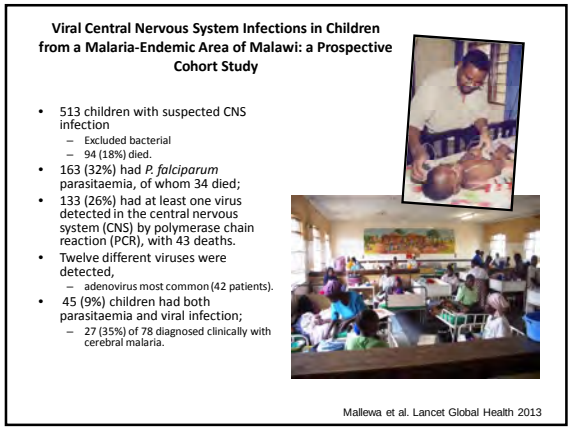

Chikungunya Virus and Central Nervous System Infections in Children, India
Fenny Lewthwaite, Ravi Vasanthapuram, Jane C. Osborne, Ashia Begum, Jenna L.M. Plank, M. Veera Shankar, Roger Hewson, Anita Desai, Nick J. Beeching, Ravi Ravikumar, and Tom Solomon
• CHIKV in plasma samples of 8 (14%) of 58 children with suspected central nervous system infection in Bellary, India.
• CHIKV was also detected in the cerebrospinal fluid of 3 children
Lewthwaite et al, EID 2009


Aedes albopictus in Europe 2008 and predicted impact of climate change
Minimal impact: short-term change scenario
Maximum impact: long-term change scenario

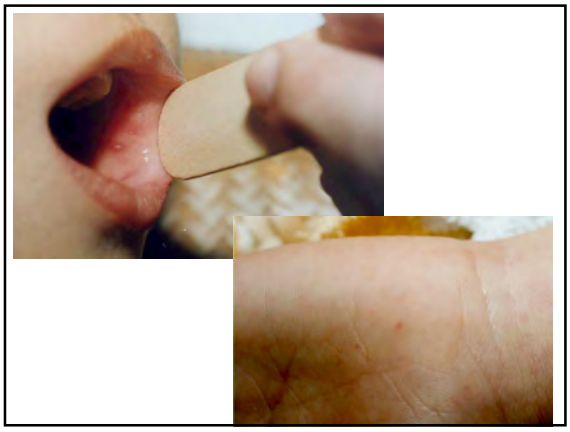



DIAGNOSTICS OF CNS INFECTIONS


Rabies is under-recognised and under-reported
Rabies encephalitis is common in Malawi and can be misdiagnosed as Cerebral Malaria - Emerging Infectious Diseases 2007, 13: 136-9


Viral Central Nervous System Infections in Children from a Malaria-Endemic Area of Malawi: a Prospective Cohort Study
• 513 children with suspected CNS infection
– Excluded bacterial
– 94 (18%) died.
• 163 (32%) had P. falciparum parasitaemia, of whom 34 died;
• 133 (26%) had at least one virus detected in the central nervous system (CNS) by polymerase chain reaction (PCR), with 43 deaths.
• Twelve different viruses were detected,
– adenovirus most common (42 patients).
• 45 (9%) children had both parasitaemia and viral infection;
– 27 (35%) of 78 diagnosed clinically with cerebral malaria.
Mallewa et al. Lancet Global Health 2013

Another Case



Human Enterovirus 71 (HEV71)

- Family *Picornaviridae*, Genus *Enterovirus*
  - Genogroups A, B(1-4), C(1-4)
  - Human Enterovirus Species A
- Isolated in 1969 California
  - stool of a child with viral encephalitis
  - Faeco-oral spread
- 1970s-80s Sporadic cases / modest outbreaks (all continents)
  - 1975 Bulgaria
  - 1978 Hungary
- Clinically
  - Hand foot and mouth disease (HFMD)
  - Neurological disease (aseptic meningitis, encephalitis, paralysis)
  - **Pulmonary oedema**

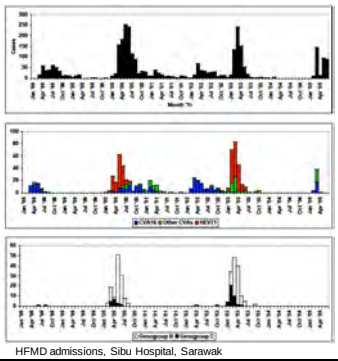
Brainstem encephalitis in EV71

T2 weighted MRI, mid saggital

Ooi MH, et al.*Clin ID* 2003

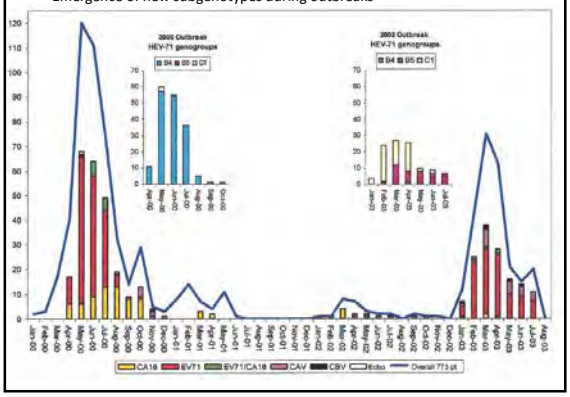
EV71 outbreaks across Asia

- 1997
  - Sarawak
- 1998
  - Peninsular Malaysia, Singapore; Japan,
  - Taiwan (**Est 1.5 million cases - Huang, NEJM,1999**)
  - Perth
- 2000
  - Sarawak, Singapore, Korea, Japan, Taiwan, Sydney
- 2001
  - Taiwan, Sydney



HFMD admissions, Sibu Hospital, Sarawak

- Emergence of new subgenotypes during outbreaks

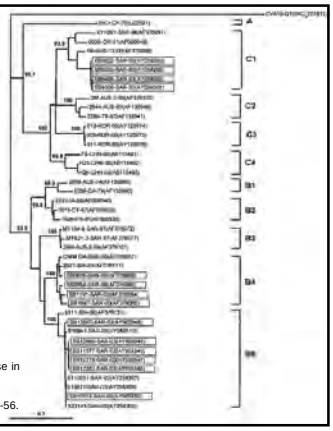


Genogroup analysis for th

HEV-71 patients

- 68 Genogroup B4
- 68 Genogroup C1
- 41 Genogroup B5 (newly emerged)

- Genogroups of HEV-71 differ ir their virulence



Ooi MH, et al. Human enterovirus 71 disease in Sarawak, Malaysia: a prospective clinical, virological, and molecular epidemiological study. Clin Infect Dis. 2007 Mar 1;44(5):646-56.

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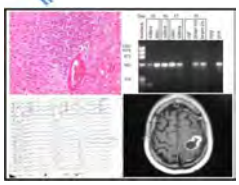
Liverpool Medical Institution



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