

## The Clinical Epidemiology of Encephalitis

### ESCMID Encephalitis Course 29-30 October 2014

**Professor Tom Solomon**  
 Director, Institute of Infection and Global Health, University of Liverpool  
 Director, NIHR Health Protection Research Unit in Emerging Infections  
 Chair of Neurology, Walton Centre NHS Foundation Trust  
 Head, Brain Infections Group  
 @RunningMadProf

- 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

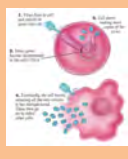


**Improving the health of humans and animals by tackling key infectious disease in both a UK and global context**

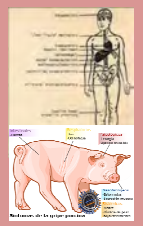
### Institute of Infection and Global Health

Director: Tom Solomon


**Department of Infection Biology**  
(Head: Jonathan Wastling)



**Department of Clinical Infection, Microbiology and Immunology**  
(Head: Nigel Cunliffe)



**Department of Epidemiology and Population Health**  
(Head: Matthew Baylis)



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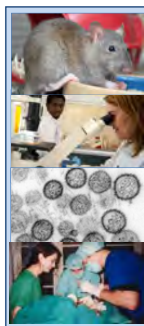
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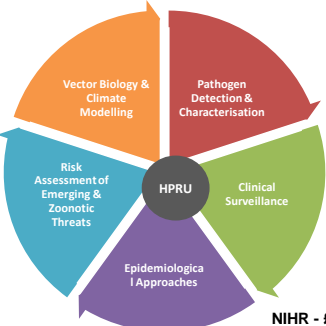
**Research Themes**

- Understanding how pathogens cause disease – Lead: Aras Kadioglu
- Pioneering diagnostics, treatments and vaccines – Lead: Neil French
- Enhancing food safety and food security – Lead: Diana Williams
- Tracking emerging and zoonotic infections – Lead: Eric Fevre
- Improving the health of pets, working animals and their owners – Lead: Alan Radford

### Emerging & Zoonotic Infections

National Institute for Health Research





**NIHR - £3.9M**

UNIVERSITY OF LIVERPOOL







Epidemiology?

## Epidemiology

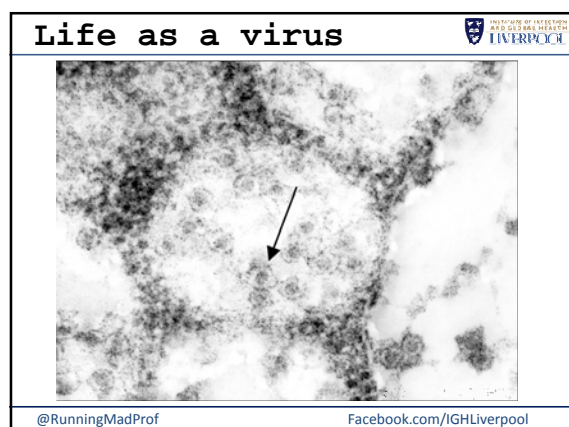
- “the science that studies the patterns, causes, and effects of health and disease conditions in defined populations.
- It is the cornerstone of public health, and informs policy decisions and evidence-based practice by identifying risk factors for disease and targets for preventive healthcare.”

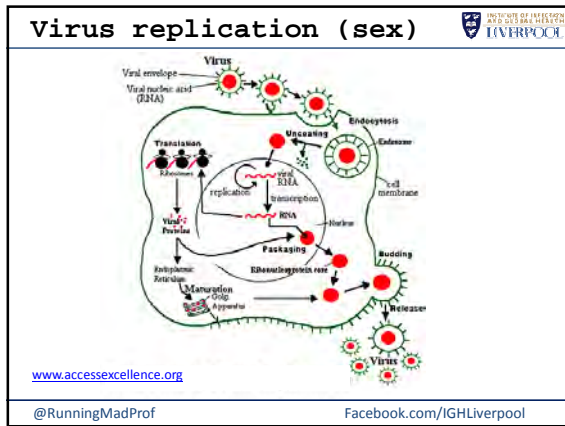
## Clinical epidemiology

- 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?





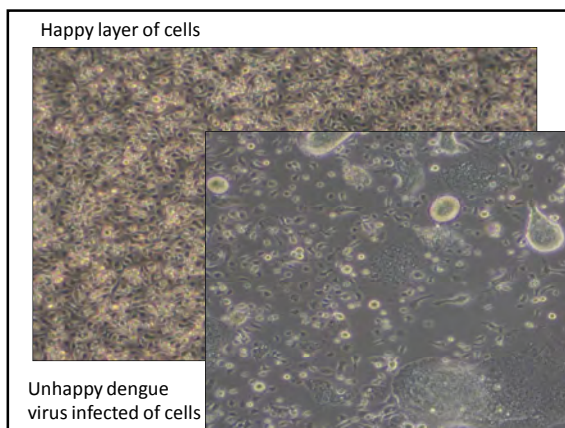
### Reproduction

10 genes

24,000 genes

The slide compares the genetic content of a virus (10 genes) to that of a human (24,000 genes). A small virus particle is shown next to the silhouettes of a woman and a man.

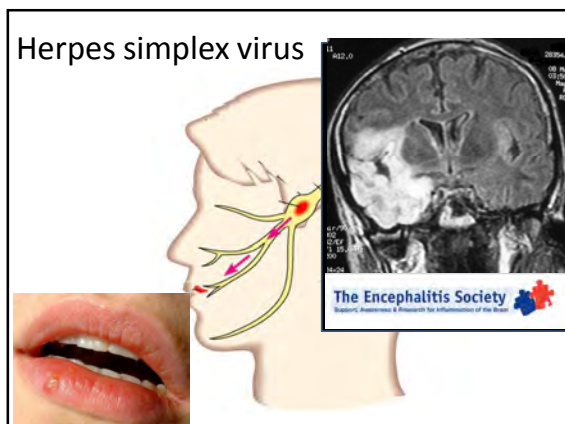
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### Viruses

Hiders and Jumpers

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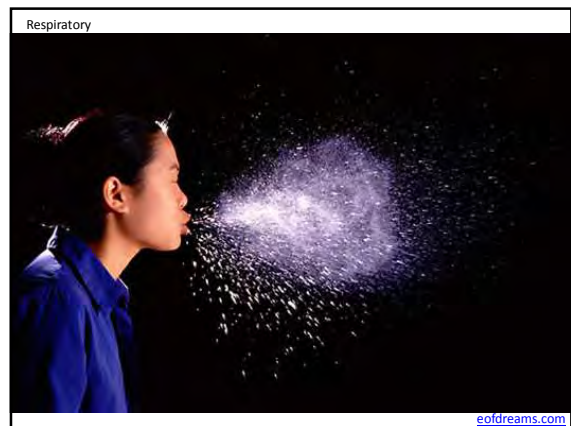
- ### Brain Infections:
- How does pathogen get into the body?
  - How does it get into the Central Nervous System?

**Jumping Viruses** 

**Routes of spread?**

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

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## 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 (arthropods)

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

www.earthintransition.org/

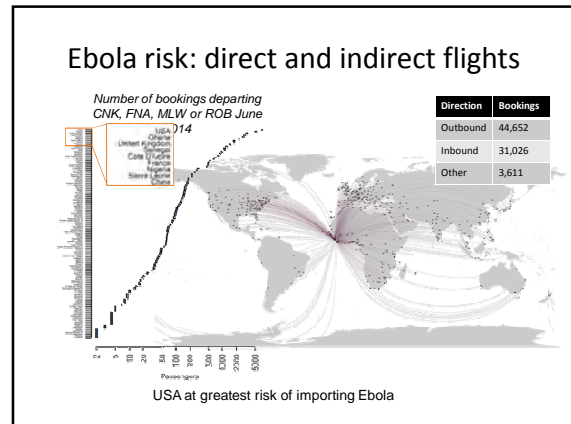
## Emerging diseases – why?

## Emerging diseases – why?

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

From: Hargrett and Kohnenova, Science, Vol. 8, 87, 1998

Airline Routes – No. Of airlines flying each route



### 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

<b>Tracking up a nerve</b> <ul style="list-style-type: none"> <li>• Herpes simplex virus</li> <li>• Rabies virus</li> </ul>	<b>Viraemia and spread across the BBB</b> <ul style="list-style-type: none"> <li>• Japanese encephalitis virus</li> <li>• Enterovirus 71</li> </ul>
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Groups	Viruses
<b>Viral causes of encephalitis</b>	
<b>Herpes viruses (family Herpesviridae)</b>	Herpes simplex virus type 1 Herpes simplex virus type 2 Varicella zoster virus type 1 Epstein-Barr virus Cytomegalovirus Human herpes virus 6 & 7
<b>Enteroviruses (Family Picornaviridae)</b>	Enterovirus 70 Enterovirus 71 Poliovirus Coxsackieviruses, Echoviruses, Parechovirus
<b>Paramyxoviruses (family Paramyxoviridae)</b>	Measles virus Mumps virus
<b>Others (rarer causes)</b>	Influenza viruses, Adenovirus, Parvovirus B19, Lymphocytic choriomeningitis virus, Rubella virus,
<b>Zoonotic viruses</b>	Rabies, other lyssaviruses Nipah virus
<b>Arboviruses (most are also zoonotic)</b>	
<b>Flaviviruses (family Flaviviridae)</b>	West Nile virus Japanese encephalitis virus Tick-borne encephalitis Dengue
<b>Alphaviruses (Family Togaviridae)</b>	Western, Eastern and Venezuelan Equine encephalitis virus Chikungunya
<b>Bunyaviruses</b>	Lacrosse virus
<b>Coltivirus</b>	Colorado tick fever
<b>Vesiculoviruses</b>	Chandipura virus


<b>CNS infections</b>	<b>Para/Post infectious causes</b>
<b>Bacteria</b>	Acute disseminated encephalomyelitis Viral (thussas with febrile convulsions) Shingles Viral infections associated with swollen tortarelle Guilan-Barre syndrome
<b>Small bacteria (mostly intracellular)</b>	<b>Non infectious diseases</b>
Mycoplasma Chlamydia Rickettsia (including scrub typhus, rocky mountain spotted fever) Ehrlichiosis Cowella (Q fever) Bartonella (Cat Scratch fever) Trophazoma whipplei (Whipple's disease) Brucellosis Typhoid fever	<b>Vascular</b> Vasculitis Systemic lupus erythematosus Behcet's disease Sub-arachnoid & sub-dural haemorrhage Ischaemic cerebrovascular accidents
<b>Spirochetes</b>	<b>Neoplastic</b>
Syphilis Lyme Neuroborreliosis Lepidospira Borrelia recurrentis (Relapsing fever)	Primary brain tumour Metastases Paraneoplastic limbic encephalitis
<b>Other bacteria</b>	<b>Metabolic encephalopathy</b>
Subacute bacterial endocarditis Listeria Nocardia Actinomyces Parameningeal infection Abscess	Hepatic encephalopathy Renal encephalopathy Hypoglycaemia Reye's syndrome Toxic encephalopathy (alcohol, drugs) Hashimoto's disease
<b>Fungi</b>	<b>Other</b>
Malaria Trypanosomiasis Amoebic encephalitis - Naegleria fowleri Cysticercosis Echinococcosis Trichinosis Amoebiasis	Drug reactions Epilepsy Hysteria Voltage gated K channel limbic encephalitis
	<b>Non-Viral causes of encephalitis and encephalopathy</b>

## 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  
**The incidence of acute encephalitis syndrome in Western industrialised and tropical countries**  
 Fidan Jmor<sup>1</sup>, Hedley CA Emsley<sup>1</sup>, Marc Fischer<sup>1</sup>, Tom Solomon<sup>1,2</sup> and Penny Lewthwaite<sup>1\*</sup>

Address: <sup>1</sup>Department of Neurosciences, University of Liverpool, Clinical Sciences Centre, Leazes Road, Liverpool, L69 7GL, (Main Submission Centre); <sup>2</sup>Department of Parasitology and Medical Microbiology, School of Tropical Medicine, University of Liverpool, Liverpool, L69 3GB and <sup>3</sup>Centre for Disease Control and Prevention, Atlanta, Georgia, USA

\*Corresponding Author: f.jmor@liverpool.ac.uk; h.a.emsley@liverpool.ac.uk; m.fischer@liverpool.ac.uk; t.solomon@liverpool.ac.uk; p.l@liverpool.ac.uk

- 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

### 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?

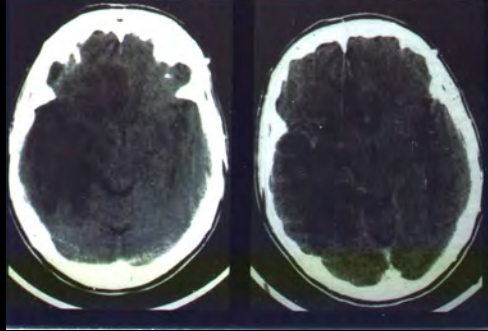
### What would you do next?

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

### Differential, Progress

<ul style="list-style-type: none"> <li>• <b>Day 1 DD</b> ?SBE, infective, tropical, ?underlying malignancy</li> <li>• <b>Day 2, SHO</b></li> <li>• DD ?Atypical pneumonia – (chest clear, sats 99%)</li> <li>• BCs, malaria film, Rx clarithromycin</li> <li>• Haloperidol for hiccoughs</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Day 3</b></li> <li>• Temp Up, Periph WCC up</li> <li>• <b>Day 5</b></li> <li>• Still headache, temp 40, voice sl slurred, v sleepy (haloperidol)</li> <li>• CT head</li> </ul>
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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

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
### 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

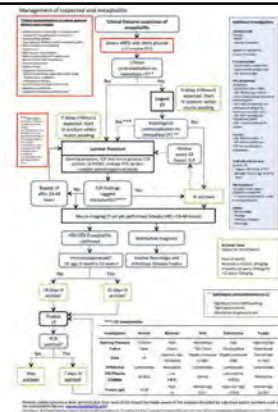


www.elsevier.com/locate/jinf

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

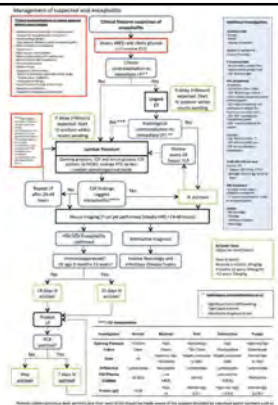
R. Kneen<sup>a,b,r,s,\*</sup>, B.D. Michael<sup>b,c,i,j,r</sup>, E. Menson<sup>d,k</sup>, B. Mehta<sup>a,j</sup>, A. Easton<sup>e,m</sup>, C. Hemingway<sup>f,n</sup>, P.E. Klapper<sup>h,o</sup>, A. Vincent<sup>h,p</sup>, M. Lim<sup>d,k</sup>, E. Carroll<sup>a,q</sup>, T. Solomon<sup>b,c,i,j</sup>, On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

Management Algorithm



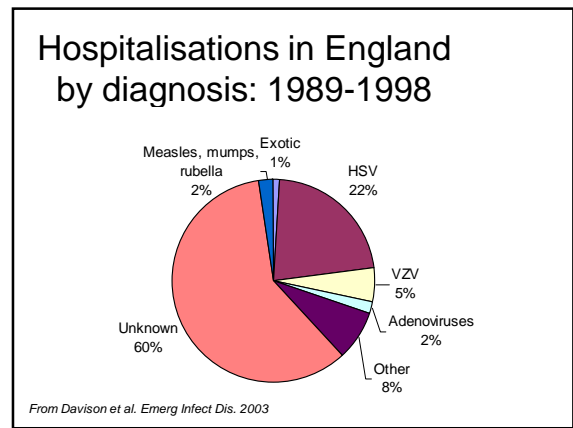
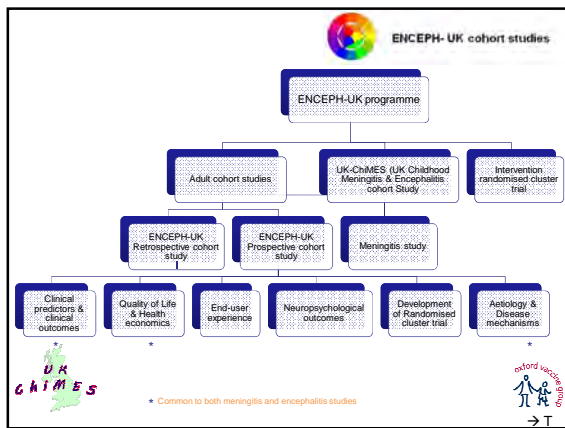
Management Algorithm

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### Understanding and Improving the Outcome in Encephalitis

National Institutes for Health Service Research (NIHR) Programme Grant



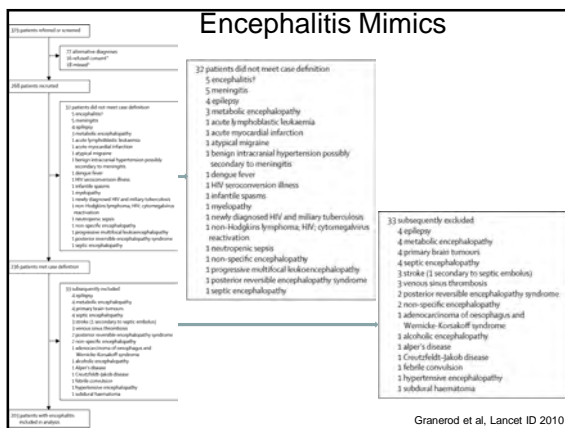
### HPA Encephalitis study

ca. Julia Granerod, Natasha Crowcroft

#### Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study

Julia Granerod, Helen E Ambrose, Nicholas W S Davies, Jonathan P Clewley, Amanda L Whitt, Elyse Morgan, Richard Cunningham, Mark Zuckerman, Kim Mutton, Tom Solomon, Katherine W Ward, Michael P Lewis, Sarah E Hone, Angela Vincent, David W G Brown, Natasha S Crowcroft on behalf of the UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group

**Summary**  
**Background** Encephalitis has many causes, but for most patients the cause is unknown. We aimed to establish the cause and identify the clinical differences between causes in patients with encephalitis in England.  
**Methods** Patients of all ages and with symptoms suggestive of encephalitis were actively recruited for 2 years (staged start between October, 2005, and November, 2006) from 24 hospitals by clinical staff. Systematic laboratory testing included PCR and antibody assays for all commonly recognised causes of infectious encephalitis, immunoglobulin for less commonly recognised causes in immunocompromised patients, and testing for travel-related causes if indicated. We also tested for non-infectious causes for acute encephalitis including autoantibodies. A multidisciplinary expert team reviewed clinical presentation and hospital tests and directed further investigations. Patients were followed up for 6 months after discharge from hospital.



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

	Immunocompetent patients* (n=172)	Immunocompromised patients† (n=31)	Total
<b>Herpes simplex virus</b>	<b>37 (22%, 16–28)</b>	<b>1 (3%, 0–1–17)</b>	<b>38</b>
Acute disseminated encephalomyelitis	23 (14%, 9–19)	..	23
<b>Antibody-associated encephalitis</b>	<b>15 (9%, 5–14)</b>	<b>1 (3%, 0–1–17)</b>	<b>16</b>
<i>Mycobacterium tuberculosis</i>	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
<i>Toxoplasma gondii</i>	..	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
<i>Listeria monocytogenes</i>	..	1 (3%, 0–1–17)	1
Pneumococcus	..	1 (3%, 0–1–17)	1
<b>Other‡</b>	<b>13 (8%, 4–13)</b>	..	<b>13</b>
<b>Unknown</b>	<b>64 (37%, 30–45)</b>	<b>11 (35%, 19–55)</b>	<b>75</b>

Granerod et al. *Lancet ID 2010*



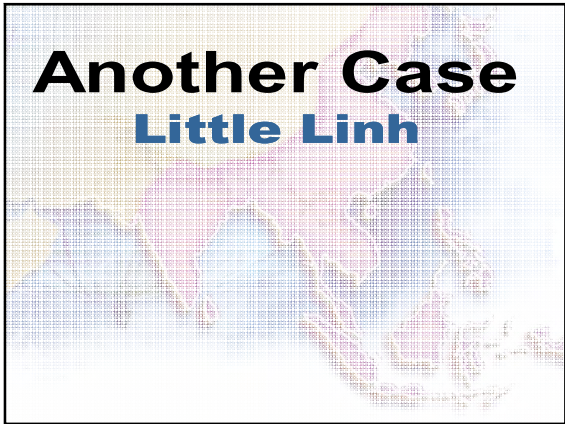
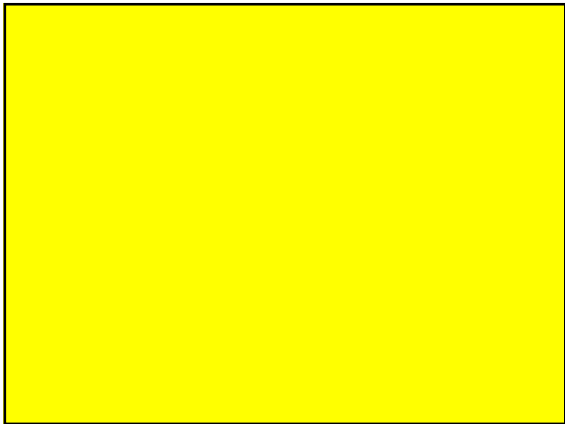
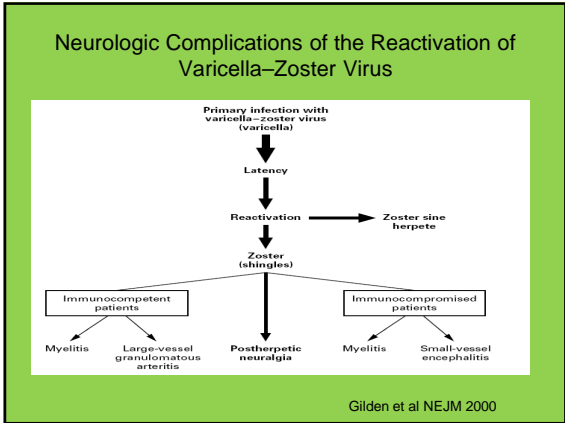
What are the clinical features of encephalitis?

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



## 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

- Temperature 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

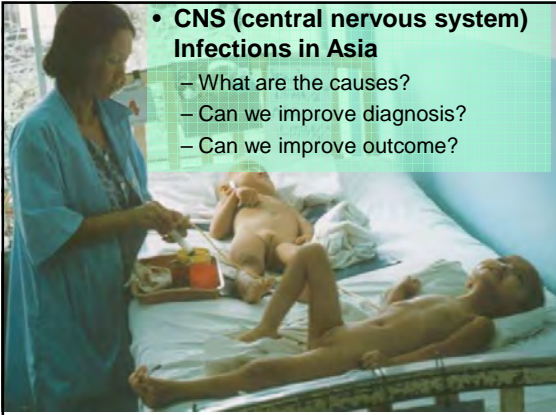
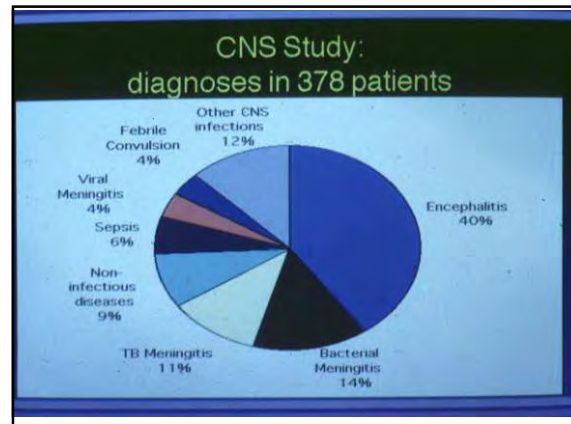
## Differential diagnosis

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

## Qn 2 List the investigations you would do?

**• CNS (central nervous system) Infections in Asia**

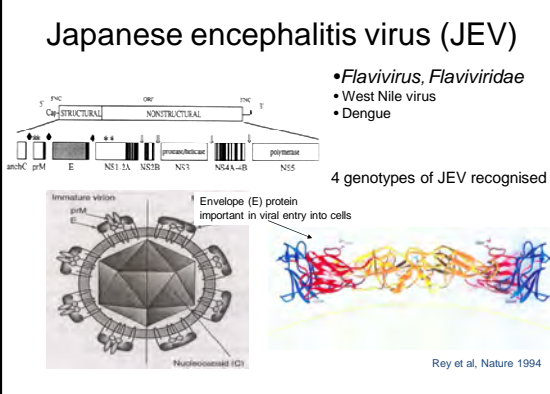
- What are the causes?
- Can we improve diagnosis?
- Can we improve outcome?

**Japanese encephalitis virus (JEV)**

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

4 genotypes of JEV recognised




Rey et al, Nature 1994



**Estimated global incidence of Japanese encephalitis: a systematic review**

Grant L, Campbell A, Susan L, Hills P, Marc Fischer A, Julie A, Jacobson S, Charles H, Hoke A, Joachim M, Hombach A, Anthony A, Marfin A, Tom Solomon S, Theodore F, Tsai T, Vivien D, Tsai T, Amy S, Ginsburg S

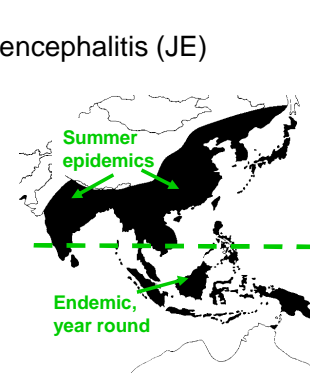
- Thirty-two areas endemic for JE in 24 Asian and Western Pacific countries sorted into 10 incidence groups
- **Approx 67 900 JE cases typically occur annually**
  - 1.8 per 100 000
  - 5.4 per 100 000 in children



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

### Diagnosis

### Diagnostic arbovirology

Diagnosis:

<b>Virus detection (limits of detection)</b>	<b>Antibody detection IgM ELISA of CSF</b>
Real-time PCR: 0.1 pfu	~50% positive by hospital admission
Virus isolation: 1 pfu	~95% positive by day 10 of illness
RT-PCR: 10 pfu	

Detection of NS1 antigen

Solomon et al BMJ 2003

### Clinical Features

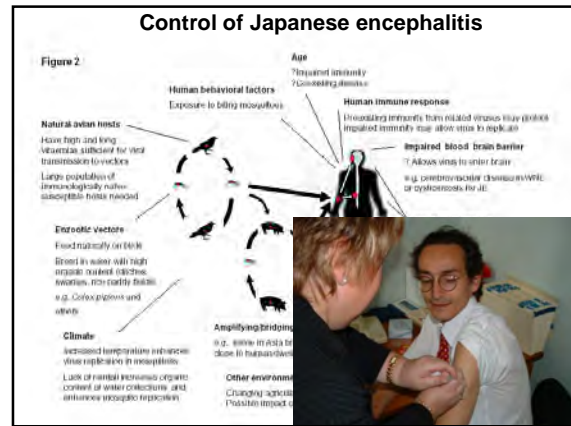
### JE: Clinical features

- Fever, headache, coma
- Convulsions\*
  - ?subtle motor Sz
- Raised ICP\*
- Polio-like flaccid paralysis
- 'Parkinsonism'
  - mask-like facies
  - cogwheel rigidity
  - tremor
- Outcome
  - 20% fatal,
  - 40% sequelae
  - 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





### Vaccines against JE

	Virus strain	Name/Manufacturer/Developer
<b>Inactivated vaccines</b>		
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
<b>Live attenuated vaccines</b>		
Primary hamster kidney	SA14-14-2	China
(Primary hamster kidney)	SA14-5-3	China
<b>Recombinant vaccines</b>		
(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.B.C.P., D.T.M.H., Ph.D.

The second half of 2005 saw one of the largest outbreaks of Japanese encephalitis that has occurred in southern India in more than 50 years. Cases were first reported in the state of Uttar Pradesh in July 2005; by November, there had been nearly 5000 cases and 1500 deaths, as well as outbreaks in neighboring Nepal. At the height of the outbreak, some hospitals had no beds available, and vast rural corridors were full of patients.

Although the number of cases was especially high for this part of India, for Asia as a whole, the outbreak was nothing new. The usual outbreaks of "summer encephalitis" were first described in Japan in the 1870s. In just six weeks in 1914, there were more than 6000 cases and 3000 deaths. The disease was initially called Japanese B encephalitis, to distinguish it from the more common St. Louis encephalitis virus, which was first isolated during the 1930s in Virginia and the United States, respectively; are genetically close to Japanese encephalitis virus and have a similar ecology and clinical features.<sup>1</sup> Dengue virus and tick-borne encephalitis virus are less closely related flaviviruses.

Japanese encephalitis virus is an arbovirus transmitted in an enzootic cycle involving birds, perennially wading animals, such as swans and egrets. Pigs can become infected and act as amplifying hosts, bringing the virus closer to human habitations—especially in parts of Asia where pigs are kept near houses. Many mosquito species are potential vectors, but only species such as Culex tritaeniorhynchus and C. tritaeniorhynchus, which breed in rice paddies and other dirty water, are especially important. Humans become infected when they are bitten by

Chapter 10

“Sadly some remarkable achievements in vaccinology have not always been matched by equal vigor in public health policy and implementation, and the disease continues to grow in importance globally.”

Newsdesk

### Gates Foundation gives \$27 million to fight Japanese encephalitis

A 5-year, \$27 million grant from the Gates Foundation will be used to tackle Japanese encephalitis—a mosquito-borne disease that has been spreading through Asia, including the Chinese, Indian, and Indonesian regions.

The vaccine in which the viral structural proteins are inserted into the yellow fever vaccine backbone. Jacobson says the programme will look at some of the virus—outside of other flaviviruses such as yellow fever, dengue fever, and West Nile virus—were first isolated in 1871. The viruses have a high fever, muscle and joint pain, and in some cases, encephalitis.

Sadly, some remarkable achievements in vaccinology have not always been matched by equal vigor in public health policy and implementation, and the disease continues to grow in importance globally. This

### A cohort study to assess the new WHO Japanese encephalitis surveillance standards

Tom Solomon, Th Thu Thuz, Penny Luvathewa, Mong Hwee Ooi, Rachel Khoo, Nguyen Minh Dang, & Nicholas White

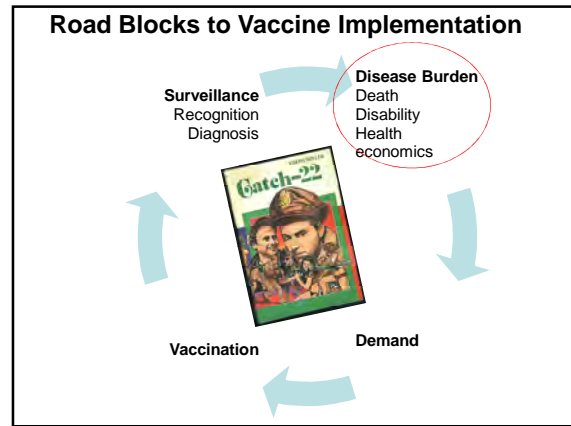
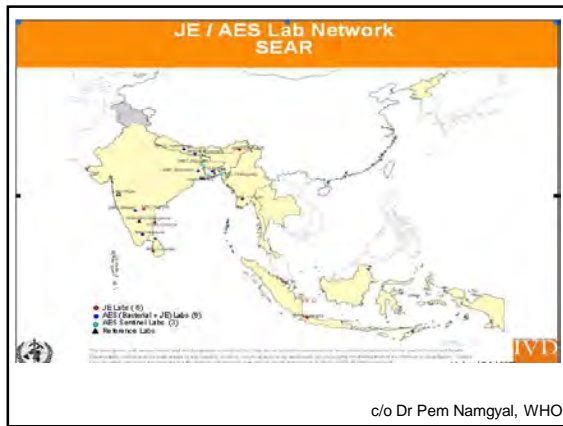
**Objective:** To assess the field use of the new WHO Japanese encephalitis (JE) surveillance standards.

**Methods:** We applied the clinical case definition of acute encephalitis syndrome (AES), laboratory diagnostic criteria and case classification to patients with suspected central nervous system (CNS) infections in southern Malawi.

**Findings:** Of the 280 patients (183 children) recruited with suspected CNS infections, 236 (85 children) met the AES case definition. Of children enrolled with CNS AES, 15 (8%) had AES, giving a sensitivity of 6% (95% CI: 2–12) and specificity of 30% (95% CI: 20–43). New adults with AES presented with AES. 19 JE-infected children missed by surveillance included 10 with acute febrile illness, two with focal neurological signs and six with meningitis only. Among the case definition, it includes both patients and meningitis improved sensitivity to 66% (95% CI: 50–82) while reducing specificity to 27% (95% CI: 15–42). Six children that did not have AES on admission had reduced consciousness after admission. Conventional JE (CJE) enzyme diagnosis seems promising together with serology analysis. Five patients with neurological manifestations of dengue infection had JE antibodies in serum and would have been misdiagnosed had we not tested for dengue antibodies in parallel.

**Conclusions:** Children enrolled with JE that presented with acute febrile illness or focal deficits only were missed by the surveillance standards, although some of them subsequently became encephalitic. A focus on the surveillance standards showing effective in these presentations would be helpful. An acute CSF sample is more sensitive and specific than an acute serum sample.

• Bulletin WHO 2008



**Japanese Encephalitis Control Partners**

Bill & Melinda Gates Foundation

GAVI ALLIANCE

CDIBP, China

PATH

UNIVERSITY OF LIVERPOOL

World Health Organization

AFRIMS

National and State Ministries of Health of 25 countries

unicef

International Vaccine Institute

International Pediatric Association

Centre for Tropical Medicine

CDC

JICA

USAID


MAHIDOL UNIVERSITY

c/o Asharna Khalakrinda



### 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?

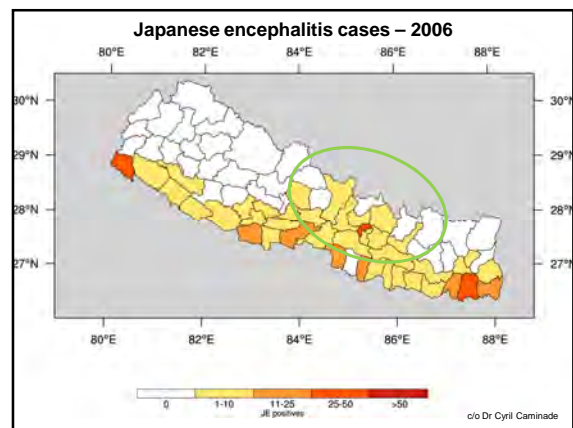
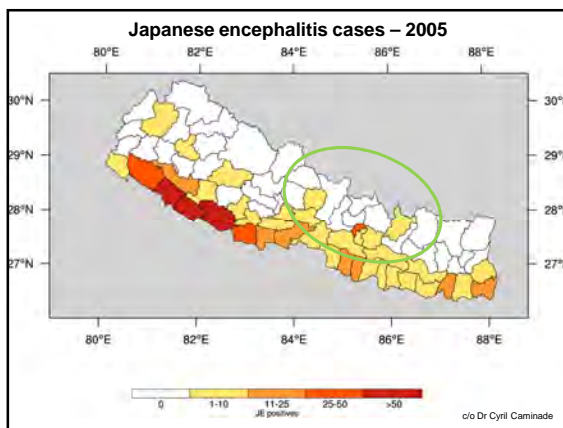
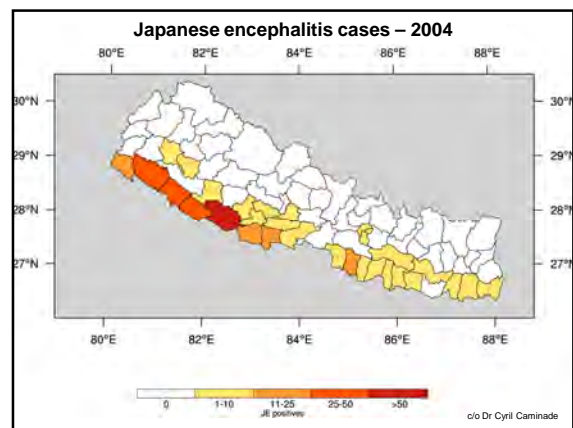
RunningMadProf Facebook.com/IGHLiverpool

### Climate Change and Japanese encephalitis

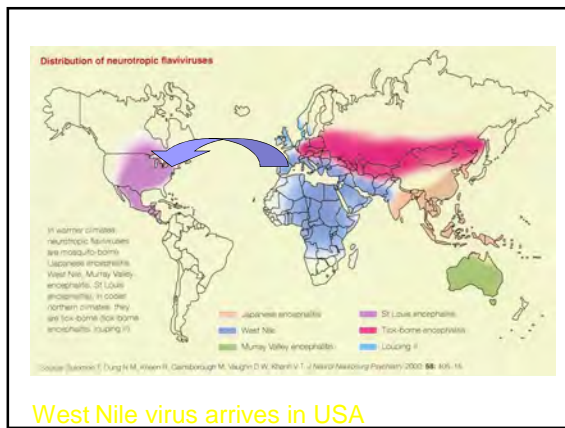
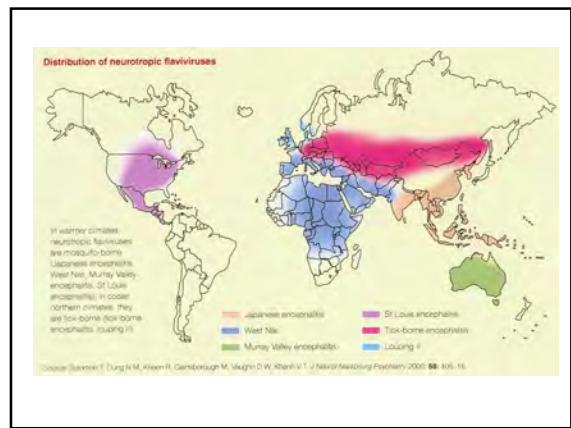
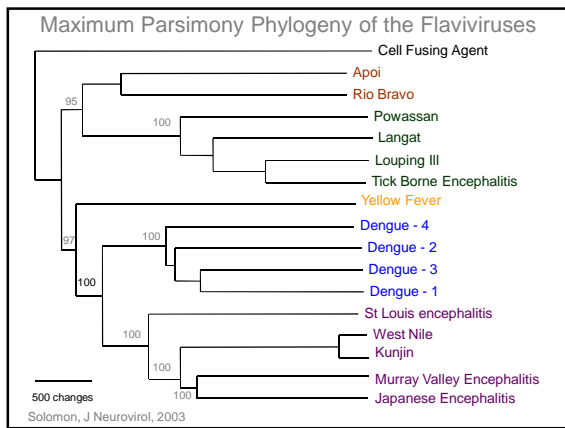
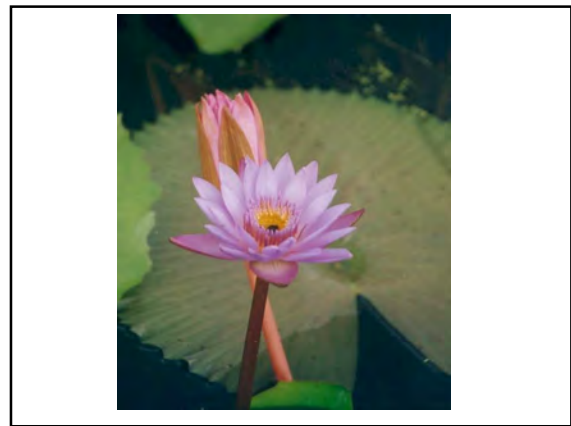
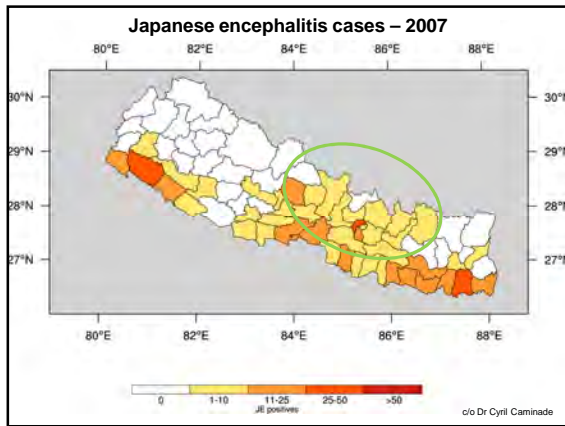




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**Welcome to Texas**

**Working in the Hot Zone: Galveston's Microbe Hunters**

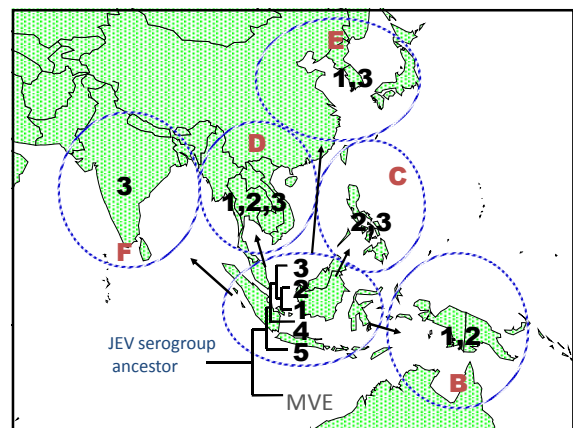
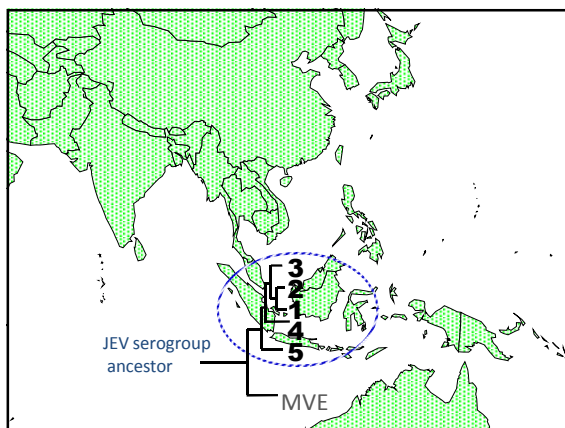
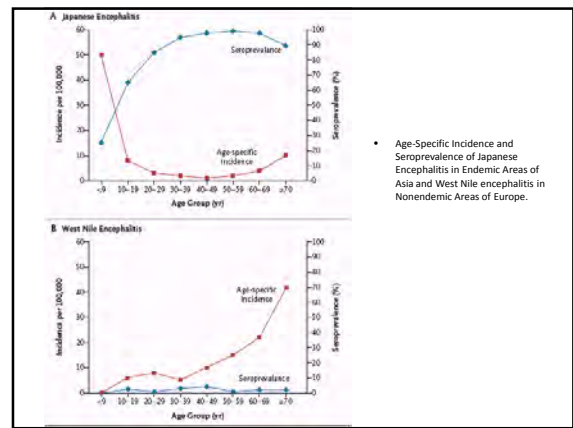
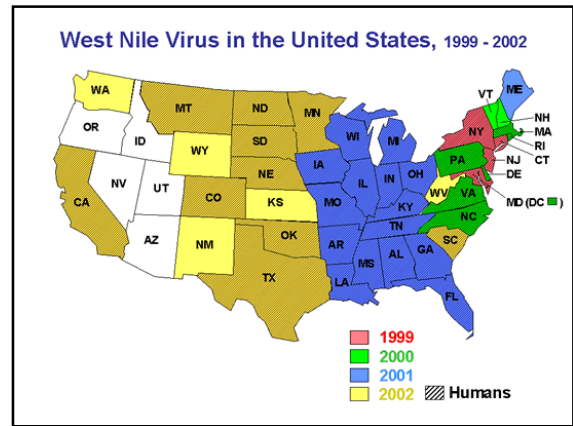
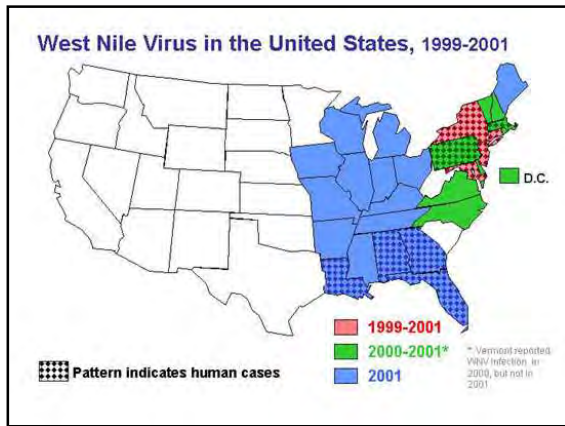
From a little-known school in a quiet Texas backwater, a world-class center for the study of infectious diseases is emerging.

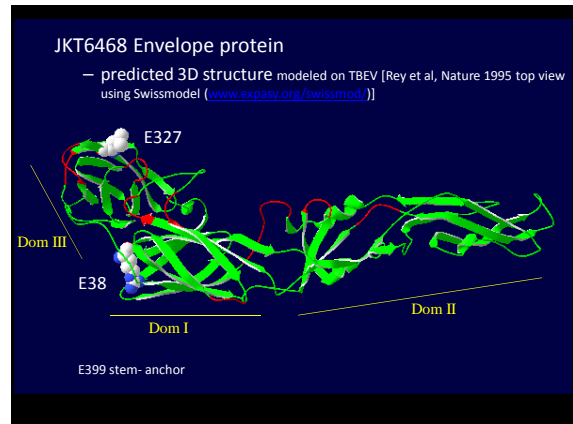
**GALVESTON, TEXAS**—When epidemiology researcher Joseph Vlastakis finished his graduate work at Johns Hopkins University 2 years ago, he had job offers from prominent universities in exciting careers that paid well. But instead, as well as year from a relatively unknown medical center in a small town in southeast Texas, he took a chance between his two options.

later from the University of Surrey in United Kingdom 2 years ago, taking the newly opened job at Galveston. "The people here were so nice and worked in the field," Galveston now seems set to be a C-13 town, a hot exchange from the state for Disease Control and Prevention.

"and that's why Vlastakis 'I chose Galveston'." "I did, in fact, come, west Galveston, people here are so nice, it's a little bit of a horror story in the field of Galveston with nothing but, study someone and a wonderful place to be in."





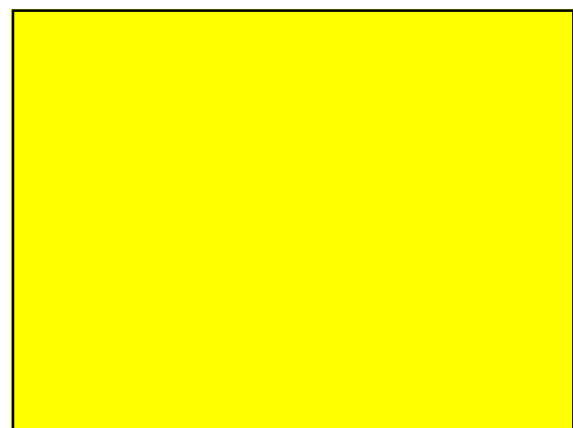


Transmission of Japanese encephalitis virus through mosquito vectors

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

Princy Leelavandri, Ravi Vasanthakumaran, Jinesh C. Dinkaran, Asha Srinivasan, Jovina L.M. Phani, M. Vaira Subashak, Roger Henson, Anish Dasak, Hira J. Deshpande, Davi Thakumar, and Tom Solomon

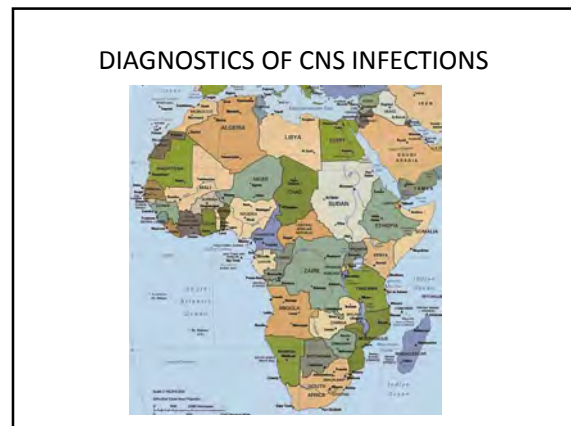
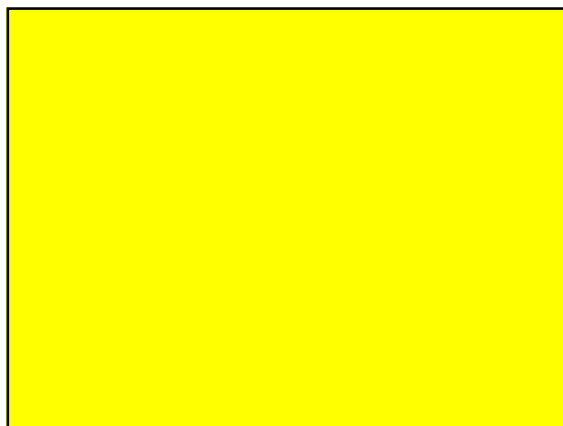
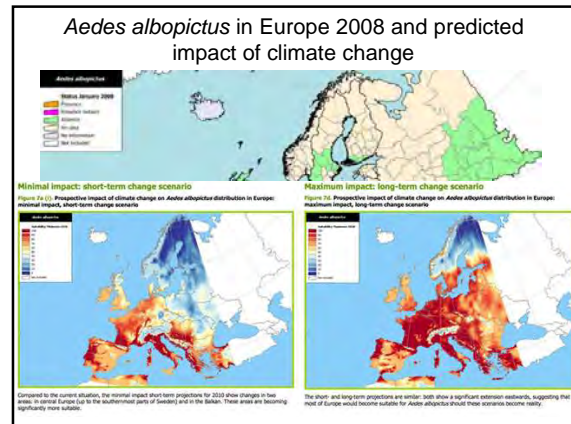
Chikungunya virus (CHIKV) is a well-circumcribed agent for causing fever, rash, and other neurological symptoms. By using the immunoprecipitation-PCR, we detected CHIKV in 8 (14%) of 58 children with suspected central nervous system infection in Bellary, India. CHIKV was also detected in the cerebrospinal fluid of 3 children.

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

**Figure 11** Digital program in an 8-month-old girl during onset of maculopapular rash was admitted to the hospital with fever, irritability, and a widespread rash. Chikungunya virus was detected in her plasma. (A) Little finger of the left hand. (B) Middle finger of the right hand, and (C) knee on the right leg.

Lewthwaite et al, EID 2009



### Rabies is under-recognised and under-reported

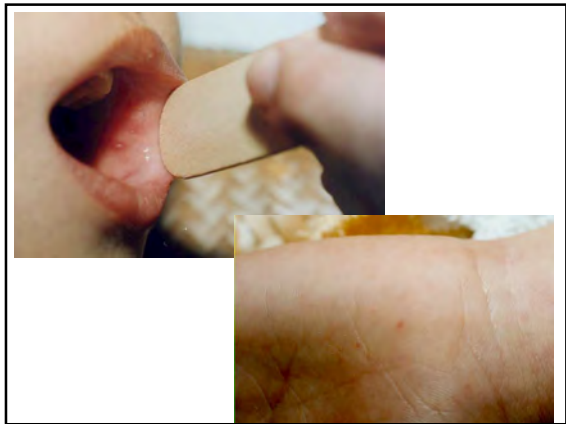
Rabies encephalitis is common in Malawi and can be misdiagnosed as Cerebral Malaria - Emerging Infectious Diseases 2007, 13: 136-9

### 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



Coi et al, Lancet Neurology 2010



### 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**

A genomic map of HEV71 showing the ORF1 and ORF2 regions. The ORF1 region is divided into three segments: VP1, VP2, and VP3. The ORF2 region is divided into three segments: VP4, VP1, and VP2. The map shows the relative positions of these segments and the overall structure of the genome.



### Brainstem encephalitis in EV71

T2 weighted MRI, mid sagittal

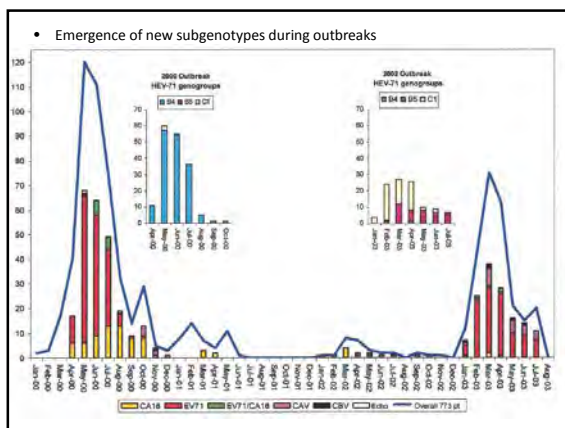
**Figure 2.** MRI changes in enterovirus 71-associated encephalomyelitis. T2 weighted images of a child aged 18 months who had presented 3 months earlier with somnolence, tachycardia, tachypnoea, and tonic, asymmetric myoclonic convulsions but remained dependent on a ventilator. High signal intensity can be seen in (A) the posterior portion of the pons and medulla (green arrows) and anterior cervical cord (white arrows) on a sagittal section, and (B) in the anterior horns of the cervical cord (green arrows) on an axial section. Modified from Shen and colleagues,<sup>14</sup> with permission of the American Society of Neuro-radiology.

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, Sibul Hospital, Sarawak

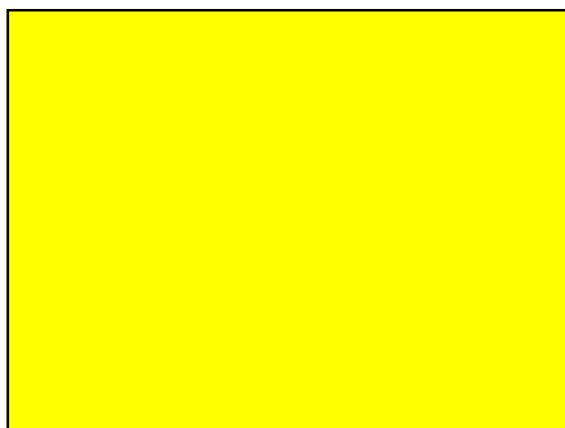


### Genogroup analysis for th HEV-71 patients

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

- Genogroups of HEV-71 differ in 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.



### Funding

UNIVERSITY OF LIVERPOOL Alder Hay Children's NHS Foundation Trust The Walton Centre NHS The Royal Liverpool and Broadgreen University Hospitals NHS LSTM

### Liverpool Neurological Infectious Diseases Course

Liverpool Medical Institution



*Feedback from previous courses:*  
"Would unreservedly recommend to others"  
"An excellent 2 days!! The best course for a long time"  
Convenors: Prof Tom Solomon, Eitan Carrol, Rachel Kneen & Dr Nick Beeching  
[www.liv.ac.uk/neuroidcourse](http://www.liv.ac.uk/neuroidcourse) email [braininfections@liv.ac.uk](mailto:braininfections@liv.ac.uk)

 **@RunningMadProf**

- -YouTube Channel: Tom Solomon
  - "Sex Drugs & Emerging Viruses"
  - Does Liverpool Have the World's Biggest Brain?



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