Unusual VIRAL causes of Childhood encephalitis

Dr Philip Britton

Senior Lecturer, Sydney Medical School (SMS)

Staff Specialist – Department of Infectious Diseases and Microbiology, CHW

THE UNIVERSITY OF SYDNEY

Viruses in May – 2018

Why study encephalitis

- **Causes:** Aetiological diagnosis frequently not made
- **Consequences**: cause of mortality, short-term survivors with significant sequelae, long-term half with cognitive/behavioural sequelae
- **'Canary in coal mine':** 'marker' syndrome for emerging and serious infectious diseases

Britton et al. JPCH 2014.
Khandaker et al. DMCN 2016.

ACE Study - methods

***D**iscovering the **I**nfectious **C**auses of unknown **E**ncephalitis (**DICE**)*

PAEDS
Paediatric Active Enhanced Disease Surveillance
ncirs
NATIONAL CENTRE FOR IMMUNISATION
apsu

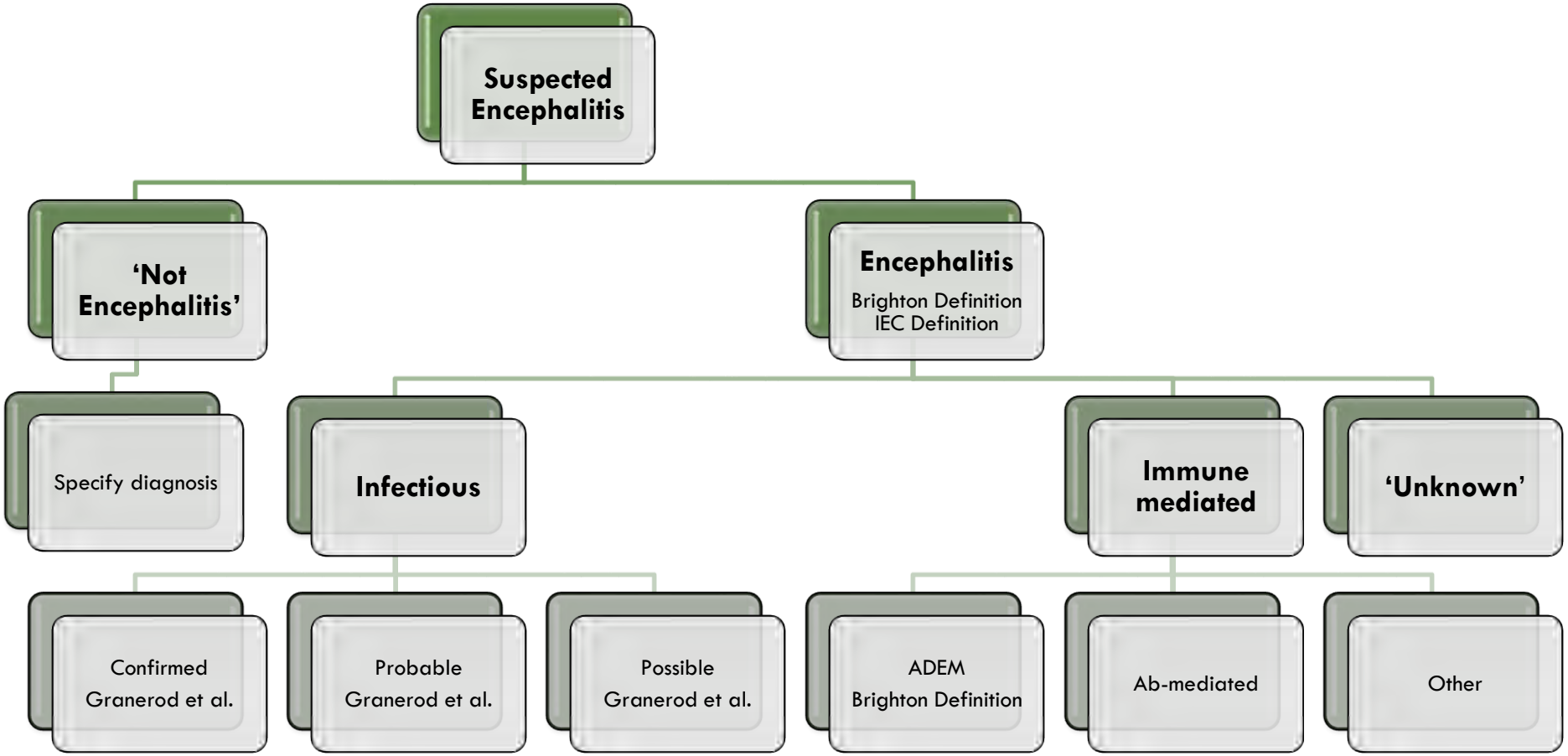
Active surveillance
"Suspected Encephalitis"

Expert clinical review
- Case categorisation
- Review diagnostics

Specimen salvaging
- Biobanking
- Novel diagnostics

Follow-up

Expert Panel - methods



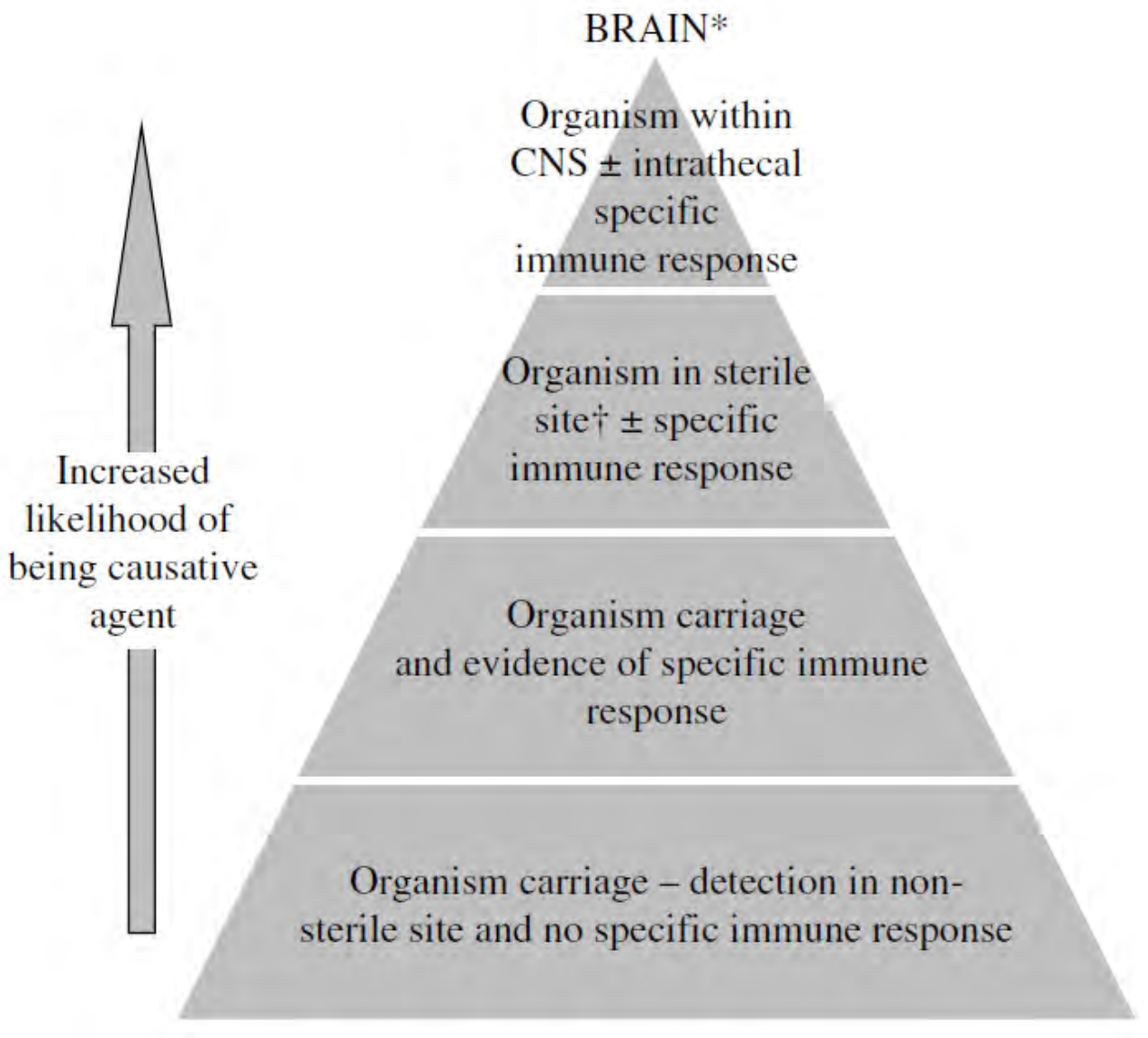
J.J. Sejvar et al.Vaccine 2007
A. Venkatesan et al. CID2013
J.Granerod et al. Epidemioll Infect. 2010

Causality

Confirmed

Probable

Possible



Granerod et al. Epi Infect 2010

‘Acute encephalitis’ - Clinical pathological spectrum

	Acute infectious encephalitis	Acute disseminated encephalomyelitis	Acute haemorrhagic leucoencephalopathy	Acute toxic encephalopathy	Septic encephalopathy
Ages	All	> 2 years	All	< 2 years	All
Antecendent infection	No	Yes	Yes	Yes	Yes
Clinical features:					
Fever	Common	Variable Uncommon in adults	Common	Common	Yes
Systemic Involvement	Sometimes	No	Yes	Sometimes	Yes
Altered level of Consciousness	Yes	Yes	Yes	Yes	Yes
Seizures common	Yes	No	No	Yes	No
Meningism	Sometimes	Sometimes	Yes	No	No
Focal CNS signs	Yes	Yes	Yes	Yes	No
Involvement of PNS	Flavivirus, CMV & EBV encephalitis	Rarely	No	No	No
CSF examination:					
↑ opening pressure	Yes	Yes	Yes	Yes	No
Pleocytosis	Lymphocyte predominant	Lymphocyte predominant	Neutrophil predominant	No	No
↑ protein	Yes	Yes	Yes	Yes (but less common in Reye’s syndrome)	Small increase in severe cases only.
Intrathecal IgG Synthesis	After 10 days	Yes, varying proportions	No	No	No
Detection of microbe by PCR	Yes	No	No	No	No
CNS imaging (CT/MRI)	Focal areas of inflammatory change	Diffuse enhancing white matter lesions	Multiple white matter lesions with haemorrhage	Diffuse cerebral oedema	Unremarkable
EEG	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Brain histopathology	Perivascular inflammation with neuronophagia & neuronal destruction	Perivenous inflammation with demyelination	Small vessel vasculitis with fibrinoid necrosis	Cerebral oedema without inflammatory infiltrate	Unremarkable

Davies et al. Jn Neuro 2006.

ACE Review Panel to end 2016 (n=519 suspected cases)

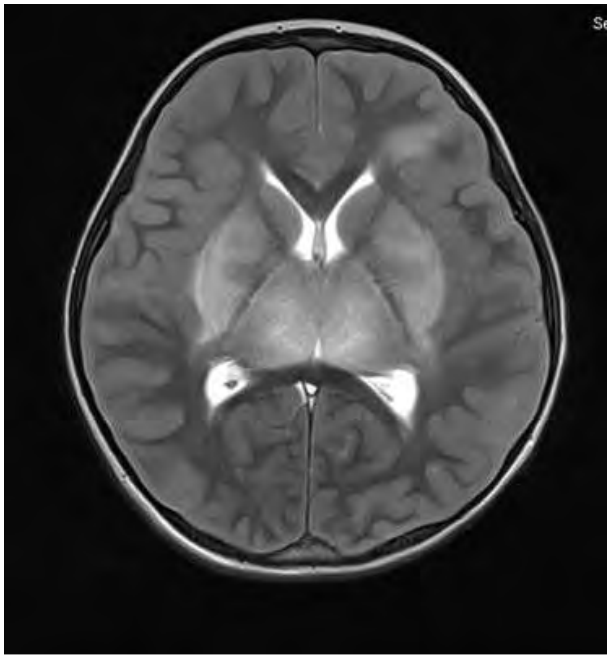
Confirmed Encephalitis (% suspected encephalitis)			285 (55)
Infectious (n (% confirmed encephalitis; 95% CI)	*Confirmed/Probable*[+] **102 (36; 30-41)**	*Possible* **59 (21; 16-25)**	***Total*** **161 (56; 51-62)**
Parechovirus	28	1	29 (10; 7-14)
Enterovirus	17	11	28 (10; 6-13)
'Bacterial'*	21		21 (7; 4-10)
Influenza		18	18 (6; 3-9)
HSV	17 (8 HSV1; 3 HSV2)		17 (6; 3-9)
Mycoplasma pneumoniae	15		15 (5; 3-8)
EBV	2		2 (2)
HHV6	1	2	3 (2)
MVEV	1	1	2 (1)
CMV	1		1 (0)
RSV		3	3 (1)
Adenovirus		2	2 (1)
HMPV		1	1 (0)
Parainfluenza		1	1 (0)
Norovirus		1	1 (0)
Rotavirus		1	1 (0)
Cryptococcus sp.		1	1 (0)
Toxocariasis		1	1 (0)
Mixed		15	15 (5)
Immune Mediated (n (%))	**73**		**73 (26; 21-31)**
ADEM	51		51 (18; 13-22)
Anti-NMDAR	17 *(2)*[#]		17 (6; 3-9)
Anti-GAD	1		1 (0)
Other^	4		4 (1)
Unknown (n (%))	**51**		**51 (18; 13-22)**

Case

3yo well boy; Asian background

- 3 days fever, cough, vomiting and diarrheoa
- Found unresponsive and cyanosed
- CT: low attenuation and swelling of the basal ganglia and upper brain stem
- CSF - WCC 1, Prot 14. 69
- AST >21,000 , ALT >11,000
- PCR positive for **Influenza A**
- Death within 48 hours of admission

Acute Necrotising Encephalopathy



IAE cases

- 23 cases of Suspected encephalitis; 13 IAE cases
  - Age: median 3.7 years (IQR1.5 –
  - Sex: 8/13 female
  - Clinical: Fever, d… …no resp.
    - 8 chil… …phalopathy
    - … 1 MERS, 1 HHS)
  - CSF …
  - Neur… …g. normal – specific syndromes
  - 1 death; 3 severe adverse
  - neurologic morbidity occurred in 7 of the 13 children (54%)

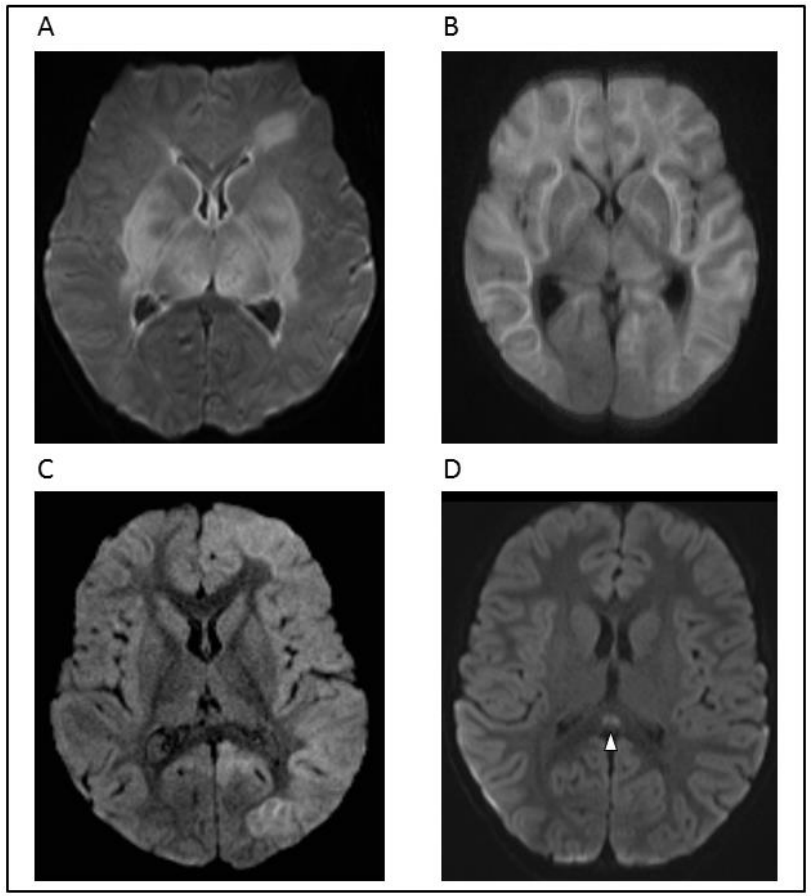
One pre-existing neurological dx
None vaccinated
15% received osteltamivir

Britton et al. *Pediatr Infect Dis J.* 2017; 36(11):1021-1026

IAE: Clinico-radiological diversity

Acute necrotising encephalopathy (ANE) Severe; mortality 25% morbidity 40%

Hemiconvulsion Hemiplegia Syndrome (HHS) Moderate-severe; mortality ?; morbidity ?70%

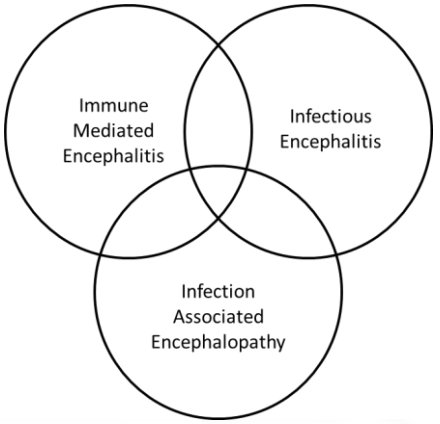


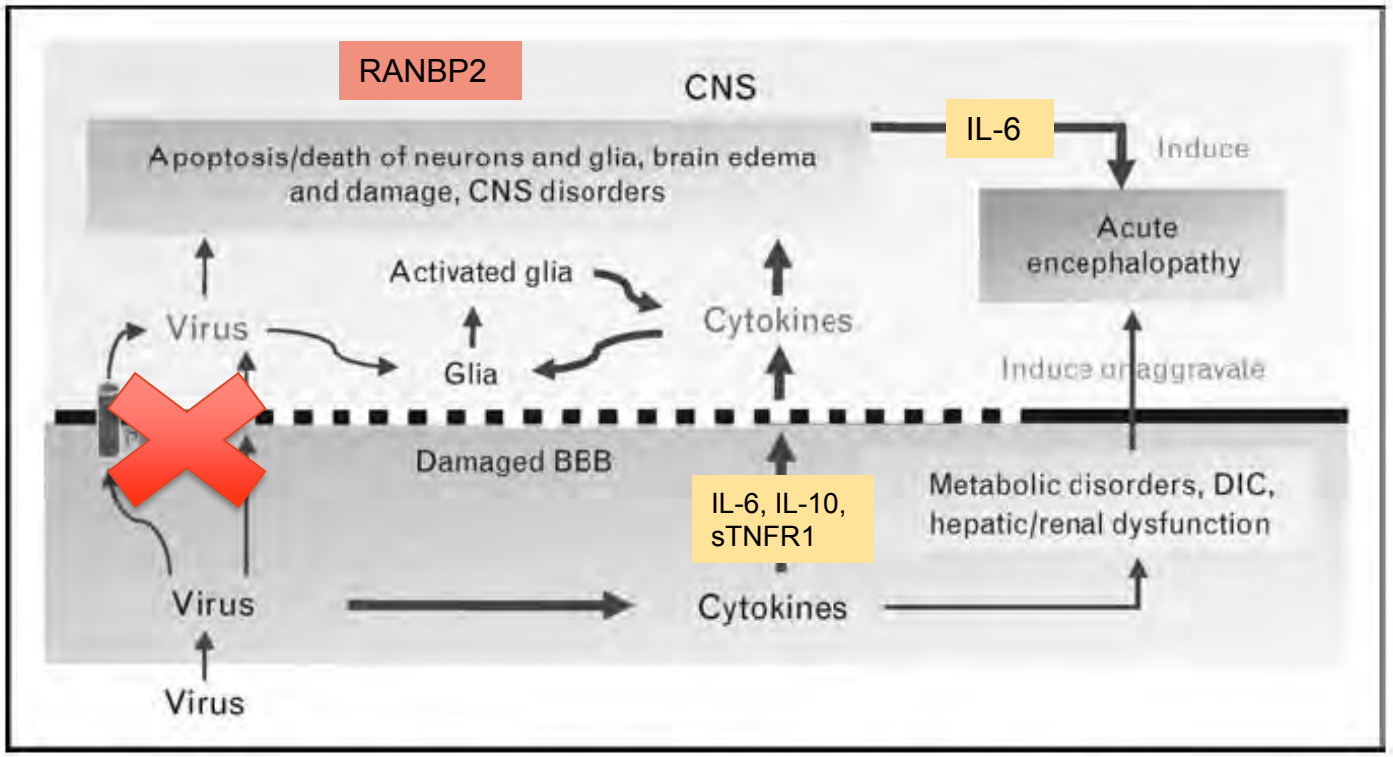
Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) Moderate-severe; mortality <5%; morbidity 70%

Mild encephalopathy with reversible splenial lesion (MERS) Mild; full recovery by 1 month

Britton et al. *Pediatr Infect Dis J.* 2017; 36(11):1021-1026

?Pathogenesis





BBB, blood–brain barrier; CNS, central nervous system; DIC, disseminated intravascular coagulation.

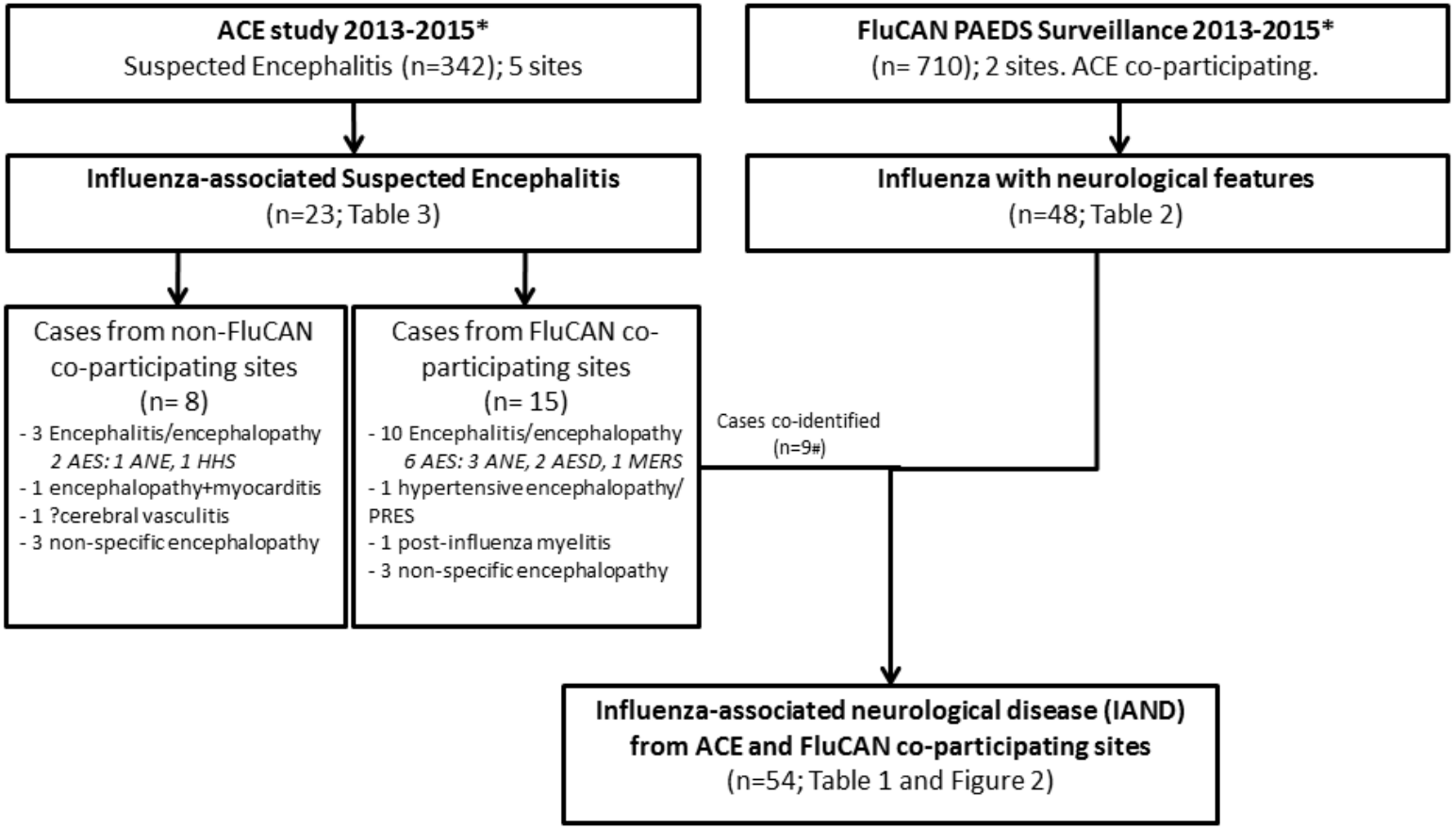
Wang et al. Curr Op in Neuro 2010; 23:305–311

ACE Outcome (short-term)

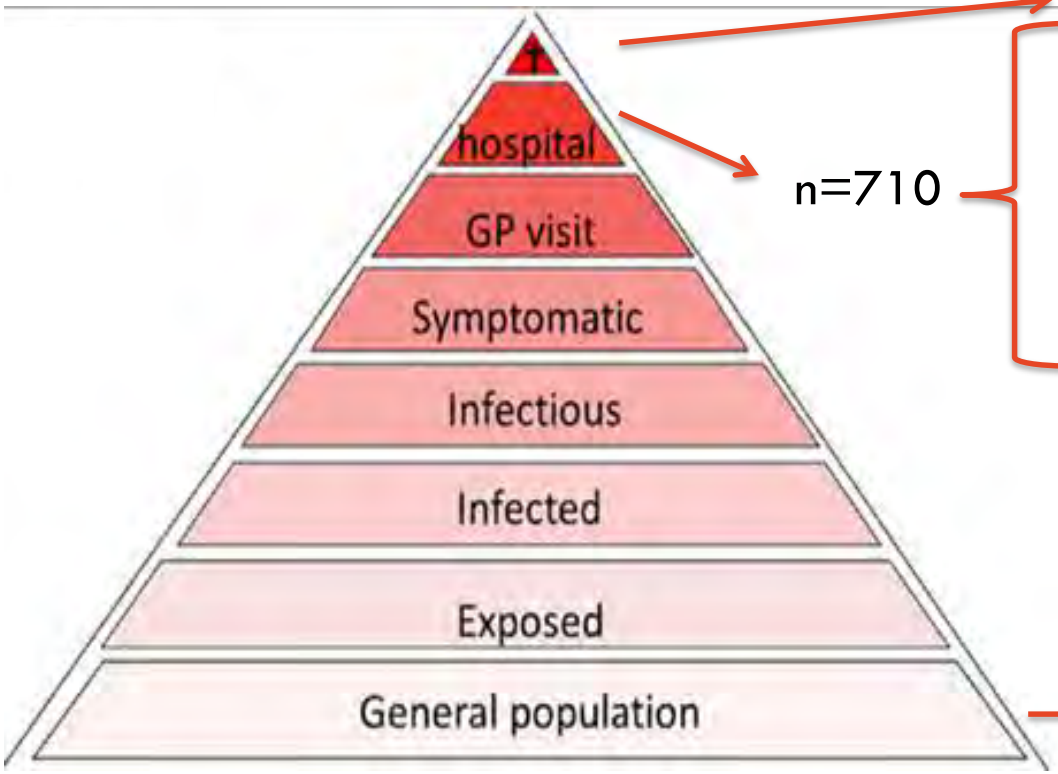
- Nine patients died (case fatality proportion 5%),
  - 7infectious encephalitis (2 influenza-associated,3 HHV6-associated, 1 parechovirus, 1 Group B streptococcus);
  - 2 with encephalitis of unknown cause.
- ICU admission occurred in 53% of cases
- Median length of stay in hospital was 9 days hospitalisation 22% of children showed moderate to severe ,neurological sequelae at discharge from hospital (Glasgow outcome scale score ≤4).

Predictor*	Multivariable aOR (95%CI)	p-value
Leading causes		**0.04**
Influenza	43.5 (3.3-500)	0.004
Anti-NMDAR	50 (4.2-500)	0.002
ADEM	6.0 (1.0-34.5)	0.04
Clinical Features		
Fever	0.18 (0.05-0.58)	0.004
GCS <13#	3.8 (1.0-7.1)	0.05
ICU Admission	7.0 (1.2-39.3)	0.02

IAND combined analysis - Methods:



Results:



n=710

Deaths n= 3

IAE n= 10

1.4 (0.5-2.3) per 100 admit

IAND n= 54

7.6 (5.7-9.6) per 100 admit

2014

0-4 yrs = 0.66 million

0-14 yrs = 1.9 million

Incidence of IAE *per 1 000 000 population*

0-4 yrs	*6.5 (1.3–20.1)*
0-14 yrs	*2.8 (0.7–7.8)*

Britton et al. *Clin Infect Dis.* 2017; 65(4):653-660

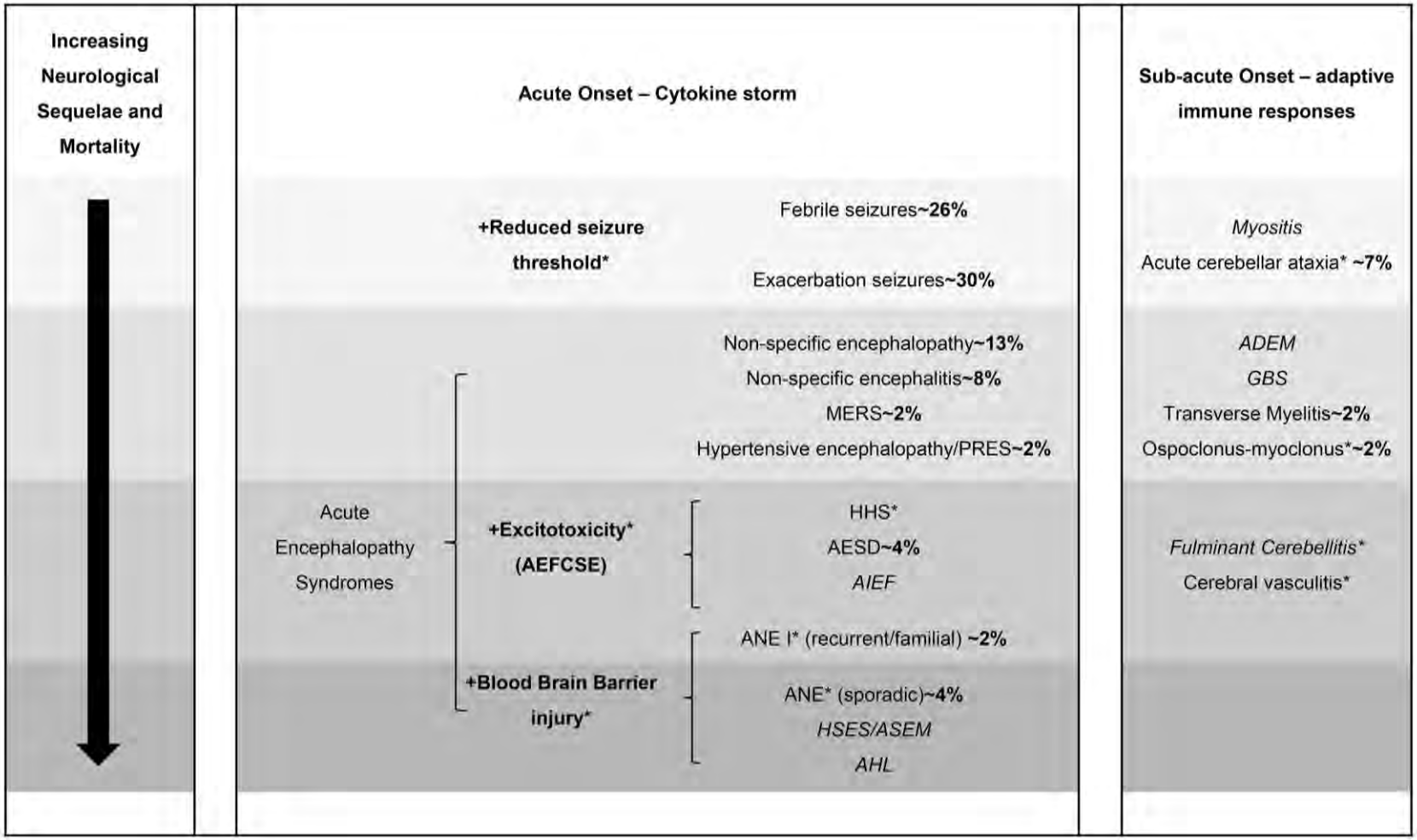
Spectrum of IAND

Table 2. Demographics, Risk Factors, Treatment, and Outcome of Influenza-Associated Neurological Disease Identified by the Australian Childhood Encephalitis Study and Influenza Complications Alert Network Surveillance, 2013–2015

Variable	Encephalitis/ Encephalopathy[a]	Other Encephalopathy[b]	Simple/Typical Febrile Seizure	Other Seizure	Acute Ataxia	Other Focal Neurological	Total	*P* Value[c]
No. (%)	10 (19)	7 (13)	14 (26)	16 (30)	4 (7)	3 (6)	54 (100)	…
Median age (y, range or IQR[d])	2.9 (1.3–6.4)	2.8 (0.1–4.9)	2.5 (1.3–4.6)	5.9 (2.1–9.6)	3.4 (1.3–10.6)	5.9 (1.0–9.2)	3.8 (1.3–6.6)	.51[e]
Aged ≤4 y	7 (70)	6 (86)	11 (79)	7 (44)	3 (75)	1 (33)	31 (63)	.21
Male sex	3 (30)	5 (71)	7 (50)	12 (75)	1 (25)	2 (67)	28 (58)	.18
Vaccinated	0	0	1 (7)	1 (6)	0	0	2 (4)	…
Preexisting neurological disease	1 (10)	2 (29)	1 (7)	13 (81)	0	1 (33)	17 (35)	**<.01**
Other medical comorbidities	0	0	4 (29)	7 (44)	1 (25)	1 (33)	13 (24)	.07
Specific diagnoses	6	1	…	…	…	3	…	…
	3 ANE	1 PRES/ hypertensive				1 opsoclonus-myoclonus		
	2 AESD					1 transverse myelitis		
	1 MERS					1 acute visual disturbance		
Influenza A:Influenza B	6:4	6:1	9:5	6:10	4:0	2:1	33:21	.16
Oseltamivir	30 (30)	1/6 (17)	3/13 (23)	2/13 (15)	1 (25)	0	8/47 (17)	.60
ICU admission	6 (60)	2 (29)	1 (7)	6 (38)	0	0	15 (28)	**.04**
Median LOS (d, range or IQR[d])	6.5 (3.5–20)	3 (2–9)	1 (1–2.3)	4 (1.3–14)	5.5 (2–20)	4 (2–10)	3 (2–8.3)	**.02**
Death	2 (20)	0	1 (7)[f]	0	0	0	3 (6)	.5
Incomplete recovery	3/8 (38)	1 (14)	0/13	5 (31)	0	1 (33)	10 (18)	.08

Britton et al. *Clin Infect Dis.* 2017; 65(4):653-660

IAND: Clinico-pathological Spectrum



Britton et al. *Clin Infect Dis.* 2017; 65(4):653-660
Goenka et al. *Clin Infect Dis* 2014; 58:775–84.

Conclusions

- IAE is associated with a high morbidity and mortality
- Influenza a possible cause of encephalitis syndrome in all children during influenza season
- Incidence of IAE comparable to that in 2009–10 pandemic and in East Asia

- IAND occurs primarily in children younger than 5 years and without preexisting neurological disease
- Specific consideration of these severe
discussion re. universal child

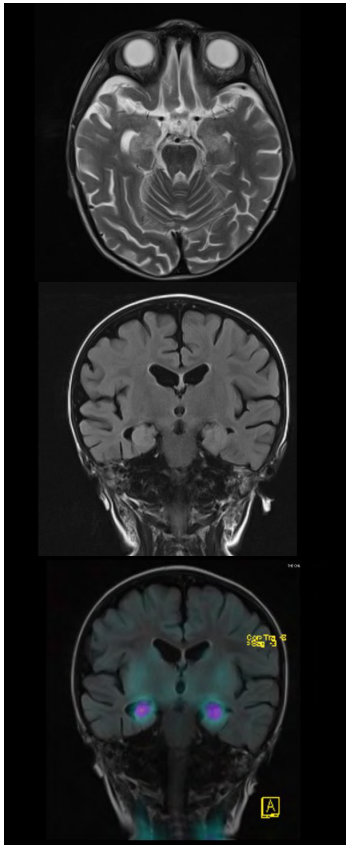
State funding for universal 'under-5' influenza vaccination from 2018

Human Herpes Virus-6 B (n=3)

8y boy Post allogeneic HSCTx ~4-5 weeks	16 mo boy, previously well	13 mo girl, previously well
Seizure, post-ictal apneoa. **MRI** – Symmetric T2 hyperintensity and diffusion restriction caudate, putamina, claustra and L hippocampus. **EEG** – abnormal **CSF** – WCC 0, prot 0.31 HHV6 pcr POS. Blood HHV6 pcr POS, then NEG on Rx. Later died	Coryzal illness then fever + seizure, irritable/ encephalopathic post, Rash. Prolonged Hypotonia and loss of skills. **MRI** – normal **CSF** – WCC , prot 0.15 CSF and blood HHV6 PCR pos	Irritability then GTCS. Prolonged coma and brain death. Deceased. **MRI** – Extensive diffusion restriction deep grey matter incl. Thalami, cerebellum, brainstem **EEG** – Generalised slowing. **CSF** – WCC 12, Prot 1.16 CSF and Blood HHV6 PCR pos (log 4.7 in blood) HHV6 IgG pos, IgM pos

NOTE: exclusion of chromosomally integrated HHV6 not undertaken in these cases

Human Herpes Virus-6 (B)



Two clear phenotypes:

- **Post Transplant Acute Limbic Encephalitis (PALE)**
  - Clinically: antegrade amnesia, insomnia, delirium, seizures
  - EEG: localised temporal lobe epileptiform discharges.
  - Imaging: localized medial temporal lobe T2, FLAIR,DWI
  - Risk: unrelated donor and cord HSCT recipients
  - Resolution of symptoms with foscarnet and ganciclovir
  - ? up to 40% mortality+ up to 80% significant neurologic sequelae
- **Primary HHV-6 associated encephalopathy/ encephalitis**
  - Up to 17% IAE in children
  - Clinically *exanthem subitum* + seizures + encephalopathy
  - Leading secondary cause of IAE clinico-radiological syndromes (ANE, AESD, AIEF, HHS etc.)

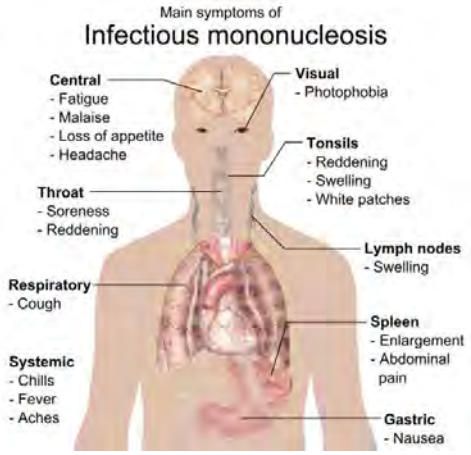
Ward KN CM et al. Arch Dis Child 2005; 90: 619–623; Mizuguchi M et al. Acta Neurol Scand 2007: 115 (Suppl. 186): 45–56

Zerr DM et al. CID 2001; **33**:763–7; Singh, N, Paterson, DL. Transplant. 2000; **69(12)**:2474-2479; Marty FM et al. Neurology. 2007; **69**:156–165; Yoshikawa T et al. JID 2002; **185**:847–53; Yamane A et al. Biol of Blood and Marrow Transplant. 2007; **13**:100-106.

Epstein-Barr Virus (n=2)

5yo boy, previously well	12 yo girl, previously well
2 day vomiting illness, GTCS on day 2 admission then 2x GTCS day 3. Irritable, combative post-ictal for 48hrs. Slowly settled. Rx with steroids. Rash. **MRI** - marked T2 hyperintensities caudate + lenitform nuclei + thalami, centrum semiovale and peritrigonal WM. Mild changes paracfalcine cortex, cingulate gyrus. No DWI **EEG** – abnormal **CSF** – WCC 2, prot 0.13 EBV IgM + heterophile Ab pos. CSF EBV PCR pos. Ev/Rhino PCR pos on nasal swab	Headache, fever, visual symptoms and papilloedema. Developed unsteady gait, intention tremor + hyperreflexia. **MRI** – peri-ventricular WM changes in occipital and R parietal lobe **EEG** – abnormal – R hemispheric slowing **CSF** – WCC 286 (97% Mono), prot 1.78 CSF EBV PCR pos. EBV IgG pos, IgM neg

Epstein-Barr Virus



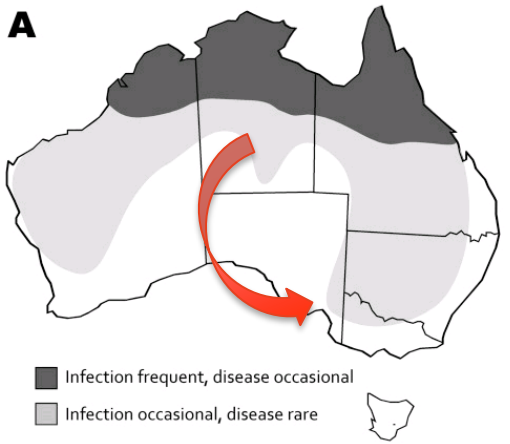
Primary EBV associated encephalitis

- **5-10%** of childhood acute encephalitis
- Pathogenesis?
- **Clinically:** meningism + progression to lethargy, disorientation and coma; radicular pain often reported
- CSF 'aseptic meningitis'; Atypical lymphocytes may be seen.
- **Diagnosis:**
  - Serology showing primary infection (EBV viral capsid antigen (VCA) IgM or EBV VCA seroconversion) **AND** EBV DNA in CSF by PCR.
  - If able EBV specific antibodies in the CSF with an high CSF:serum ratio may increase the specificity
- **MRI** can be normal; basal ganglia and cerebellar lesions
- Acyclovir is not recommended.
- Majority recover fully, occ. severe adverse outcomes

Doja A et al. J Child Neurol. 2006;21(5):385-391; Volpi A. Herpes 2004;11S2:120A-127A; Mazur-Malewska K et al. J Child Neurol 2016; 31(6):700-8; Hausler M et al. J Med Virol 2002; 68(2):253-63.

Murray Valley Encephalitis Virus cases (n=2)

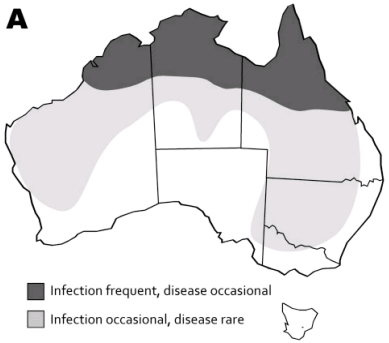
8y boy	2mo girl
Fever, seizures, reduced LOC, lower limb spasticity **MRI** - "Diffuse meningeal enhancement + basal ganglia and **bilateral** thalamic diffusion restriction **EEG** - abnormal **CSF** – WCC 388, prot 0.86 MVEV IgM pos (IgG neg)	'Septic', status epilepticus, flaccid quadriplegia, CN palsies, oral dyskinesia **MRI** - "Focal **unilateral thalamic** + rostrum CC diffusion restriction" **EEG** - abnormal **CSF** – WCC 156, prot 2.4 MVEV IgG and IgM pos. CSF MVEV IgM neg.



Both children with severe neurological sequelae at discharge

Endemic Flaviviruses

	Murray Valley Encephalitis Virus (MVEV)	Kunjin Virus (KUNV/WNV)
Virus Vector	*Flaviviridae; JEV serogroup* *Culex annulirostris*	*Flaviviridae; JEV serogroup;* WNV-like *Culex spp.*
Ecology + epidemiology	Enzootic: mosquito-water bird cycle in Northern Australia; mammals as amplifiers Epizootic: SE + SW Australia ?climactic factors	
Frequency	0-2 cases pa since 2001 *except* 2001(6); 2009(4); **2011 (16)**	0-3 cases pa since 2001 *except* 2001 (5); 2003 (9); 2004 (6). Outbreak in horses in NSW 2011
Clinical	~1% infections = disease. JEV-like. mortality 30%; young children at ↑ risk	Similar to MVE but less severe, no deaths. FAR syndrome.



Knox, MJA 2012; Frost, EID 2012;
Gray, Am Jn Trop Med Hy 2011;
Speers, Am Jn Trop Med Hy 2013

Testing in the ACE study cohort

– 'Arbovirus' testing = **flavivirus** (+/- alphavirus)

	Suspected Encephalitis N=324	Not encephalitis N=130	Encephalitis with known cause N=156	Unknown encephalitis N=38	*p-value
Arboviral serology tested	25/308 (8%)	4/119 (3%)	15/143 (12%)	6/36 (17%)	0.45
Arboviral testing positive	2/25 (8%)#	0	2/15 (13%)#	0	

*Fisher exact testing comparing proportion tested in the encephalitis with known cause and unknown encephalitis groups.

Neuroimaging & Exposure history in untested, 'Unknown' encephalitis

- MRI performed in 29 of 30 cases.
- MRI abnormal "consistent with encephalitis" in 18/29
  - With thalamic involvement: **n=5**
  - With other basal ganglia involvement: **n=3**

28%

- Mosquito bites: 2 of 30 (7%) cases

- Travel OS: 4/8 of 30 (27%) cases
  - 1 Bali 2/52 prior
  - 1 Malaysia 3 mo prior
  - 1 Hawaii 5 mo prior
  - 1 Pakistan *nos*

13%

Rotavirus

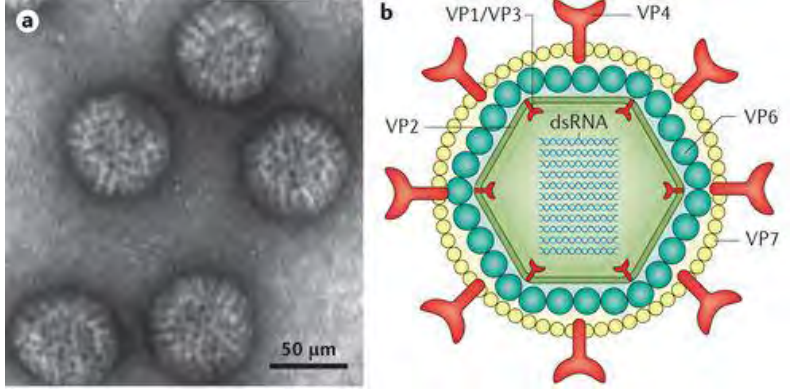
12 yo boy, previously well

Fever, diarrheoa and vomiting. GTCS. Confused, 'delirious'
>24hrs post
Clinically dehydrated – but not electrolyte disturbance

CT normal
CSF – WCC 3, Prot 0.17

Other Ix – CSF HSV, EV, Adeno PCR neg. Resp viral – neg. Stool Ev/Adeno/noro neg. **Rota pos.**

Rotavirus



- Since 1980's – seizures (afebrile) and encephalopathy in the context of acute gastroenteritis
- Up to 10% Rotavirus GE with seizures; 6% encephalopathy
- >75% outcome benign; occ. death
- Published cases with:
  - CSF pleocytosis
  - CSF rotavirus NA detection - ?contaminant
  - CSF rotavirus Ab detection

- More recently specific clinic-radiological phenotypes:
  - **MERS**
  - HHS
  - 'Cerebellitis'
  - Reye Sx

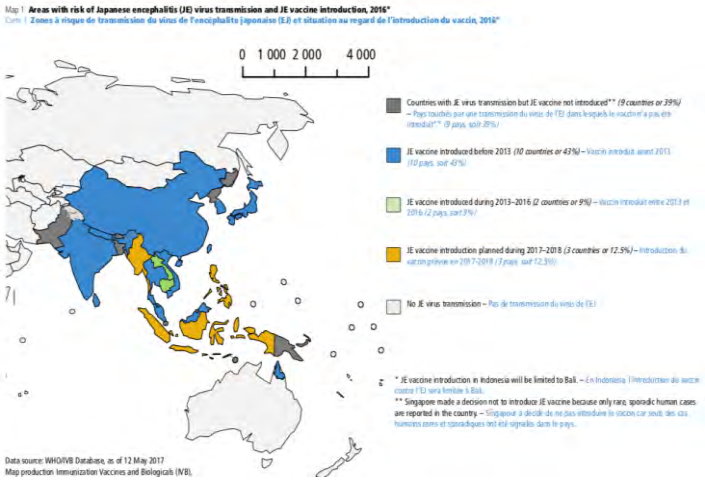
Dickey M et al. Pediatr Infect Dis J 2009;28: 318–321;
Karampatsas K et al. PLoS ONE 13(3): e0194009;
Hattori F et al. Pediat Int. 2018;60(3):259-263;
Karampatas K et al. BMC Infect Dis 2015;15:446;
Yeom JS et al.. Neurology 2015;84(1):21-7;
Kawamura et al. Brain Dev. 2014;36(7):601-7.

Emerging and re-emerging

- Australian encephalitides:
  - Murray Valley Encephalitis (MVEV)
  - WNV/Kunjin Virus (KUNV)
  - **Australian Bat Lyssavirus (ABLV)**
  - **Hendra virus**
- Regional threats:
  - Rabies (RABV)
  - JEV
  - Dengue
  - Nipah
  - CHKV

Britton et al. JPCH 2014
Britton et al. ID-DT 2014

Japanese Encephalitis Virus



'encephalitic' Flavivirus

- 11-69% childhood encephalitis in Asian cohorts
- almost 70,000 cases in Asia annually
- Up to 185 per 100,000 per year; 75% <15y

- **Clinical:** Specific features associated with JEV encephalitis include a Parkinsonian movement disorder, and weakness, be it bulbar or limb
- **Diagnosis:** serum AND preferably CSF for JEV-specific IgM. CSF PCR relatively insensitive
- **MRI:** signal in the thalami, substantia nigra and basal
- No effective treatment;
  - trials of ribavirin, interferon-alpha and dexamethasone have shown no benefit
- **Outcome:** CFR 20-30% and moderate-severe sequelae up to 40%
  - Risk Factors associated with worse outcome: younger age, greater impairment LOC, dystonia, focal neurologic signs
- Vaccine preventable, but not all countries undertake surveillance and/or have immunization programs (WHO)

Britton et al. Infect Dis–Drug Targets 2014; Rayamajhi, A et al. BMC Infect. Dis 2011; 11:294-306. Misra, U.K et al. Neurol. India 2003; 51: 55-9; Handique, S.K et al. Am. J. Neuroradiol 2006; 27: 1027-31. Dung, N.M et al. J. Neurol 2009; 256:2052-60; Kumar, R et al. CID 2009; 48: 400-6; Solomon, T et al. Lancet 2003; 361:821-6. Hoke, C.H. Jr et al. JID 1992; 165:631-7; Hills, S.L et al. J. Trop. Pediatr 2011; 57:241-4; Maha, M.S et al. Int. J. Infect. Dis 2009; 13:e389-e393; Kamala, C.S et al. Indian Pediatr. 1989; 26:445-52. Labeaud, A.D et al. Popul. Health Metr 2011; 9:1-11; Heffelfinger JD. WHO Weekly Epi Rec. 2017; 92:321–332

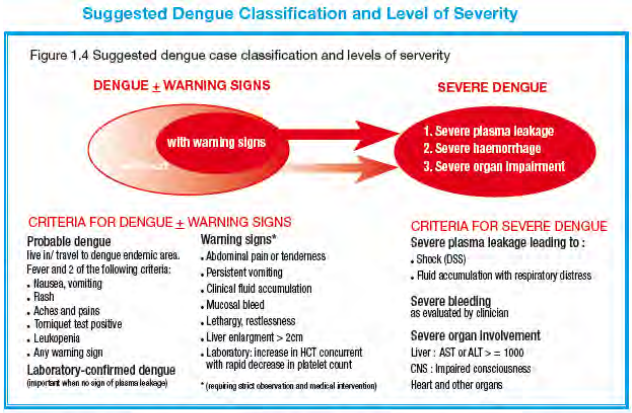
Dengue

'non-encephalitic' Flavivirus

- FAR + Haemorrhagic fever
- 2-28% of childhood encephalitis in Asian cohorts; 0.5-21% of hospitalized Dengue

- Encephalopathy - indirect mechanisms BUT evidence of detection of Dengue virus within the CNS from clinical and autopsy studies
- CSF pleocytosis + absence of liver failure, metabolic derangement or intracranial haemorrhage **differentiate encephalitis from encephalopathy**

- **Clinical:** Altered LOC, seizures, limb rigidity/weakness
- **Diagnosis:** serum AND CSF specific IgM, and blood/CSF for Dengue RNA by PCR and/or NS1 antigen.
- **Outcome:** In small series, majority fully recover; death and neurological sequelae described



Source: World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control - New Edition 2009. WHO: Geneva; 2009

***Panel 2:* Proposed definitions for neurological features of dengue**

Dengue diagnostic test highly suggestive of or confirming acute dengue virus infection, as recommended by WHO*, AND one of the following clinical categories:

Dengue CNS involvement

At least one of the following: impaired consciousness (for children younger than 6 years, Blantyre coma score ≤4; for those older than 5 years, Glasgow coma score ≤14), neck stiffness, focal neurological signs, or seizure

Dengue encephalopathy

- Dengue CNS involvement, AND
- Presence of one of the following dengue-associated complications: hepatic failure, metabolic acidosis, severe hyponatraemia, prolonged shock, disseminated intravascular coagulation, or brain haemorrhage, AND
- Normal CSF (in brain haemorrhage, blood in CSF is possible)

Dengue encephalitis

- Dengue CNS involvement, AND
- Presence of dengue virus RNA, IgM, or NS1 antigen in CSF, AND
- CSF pleocytosis without other neuroinvasive pathogens

Immune-mediated dengue CNS involvement

Other or non-specified dengue CNS involvement

Dengue-associated neuromuscular complications

- Guillain-Barré syndrome
- Rhabdomyolysis
- Other or non-specified peripheral neuromuscular complications

Dengue-associated neuro-ophthalmic complications

- One of the following clinical symptoms: blurred vision, eye flashes, floaters, sudden decrease in vision, visual field defect, scotoma, eye redness, metamorphopsia, or micropsia, AND
- Eye examination with at least one of the following: optic neuropathy (optic disc swelling or hyperaemia), maculopathy (oedema or blot haemorrhages), retinal vasculitis, retinal haemorrhages, exudative retinal detachment, cotton wool spots, or signs of foveolitis or anterior uveitis

Britton et al. Infect Dis–Drug Targets 2014; 14:78-88; Halstead, S.B. Lancet 2007; 370: 1644-52; Carod-Artal, FJ et al. Lancet Neurol., 2013; 12:906-19; Solomon, T et al. Lancet, 2000; 355: 1053-9; Misra, U.K. J. Neurol. Sci 2006; 244: 117-22.

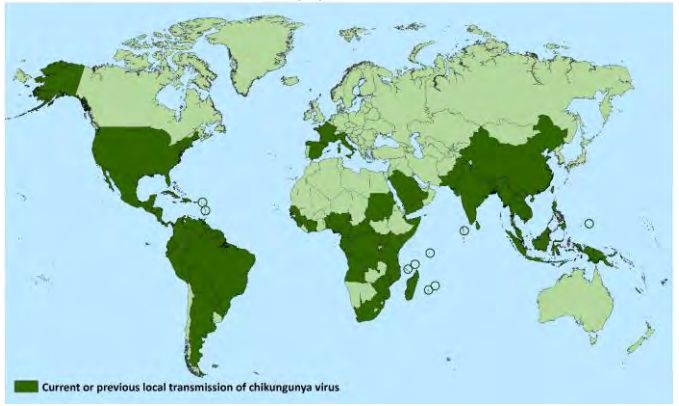
Chikungunya

alphavirus from family *togaviridae*

- Most commonly - fever, arthralgia, rash with potential chronic arthritic disease

- Up to 10% of CHKV infections in adults associated with encephalitis
- La Reunion island outbreak 2005-6 - 30 children, 12 encephalitis (decreased consciousness/seizures/focal neurological signs)
  - 2 died, 5 neurological sequelae at 6 months
- **Diagnosis:** positive PCR or IgM in blood AND positive PCR in CSF

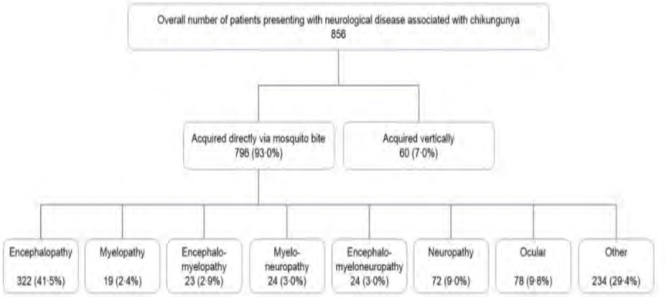
Countries and territories where chikungunya cases have been reported*
(*as of April 25, 2018*)



*Does not include countries or territories where only imported cases have been documented.

Data table: Countries and territories where chikungunya cases have been reported

AFRICA	ASIA	AMERICAS	
Angola	Bangladesh	Anguilla	Panama
Benin	Bhutan	Antigua and Barbuda	Paraguay
Burundi	Cambodia	Argentina	Peru
Cameroon	China	Aruba	Puerto Rico
Central African Republic	India	Bahamas	Saint Barthelemy
Comoros	Indonesia	Barbados	Saint Kitts and Nevis
Cote d'Ivoire	Laos	Belize	Saint Lucia
Dem. Republic of the Congo	Malaysia	Bolivia	Saint Martin
Djibouti	Maldives	Brazil	Saint Vincent & the Grenadines
Equatorial Guinea	Myanmar (Burma)	British Virgin Islands	Sint Maarten



Presentations of nervous system disease associated with chikungunya infection

Britton et al. Infect Dis–Drug Targets 2014; 14:78-88; Burt, FJ et al. Lancet 2012; 379: 662-71; Chandak, N.H et al. Neurol. India 2009; 57: 177-80; Robin, S et al. J. Child Neurol 2008; 23: 1028-35; Robin, S et al. J. Child Neurol 2008; 23:1028-35; Mehta R et al. Rev Med Virol. 2018;28:e1978.

Guideline for Australia and New Zealand

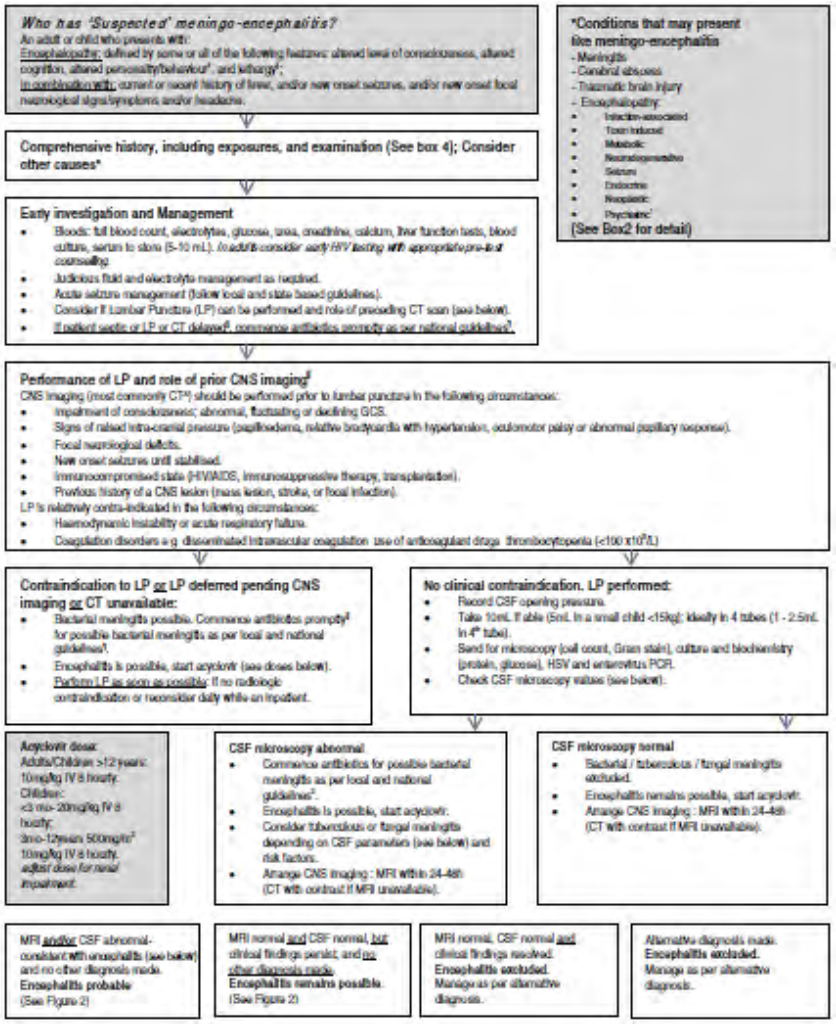
Britton, Jones, Booy , Dale et al.

On behalf of ASID Clinical Research Network Encephalitis SIG, PHAA, ANZAN, ACEM

Algorithm 1:

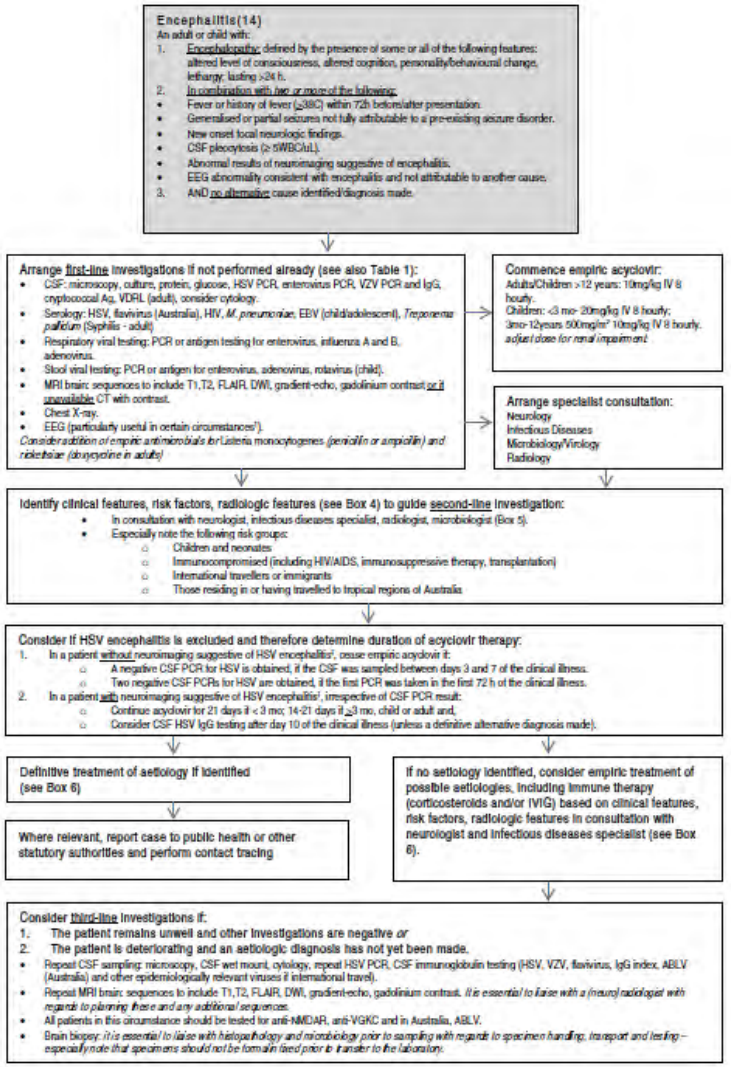
'Suspected Menigo-encephalitis'

- ↑ sensitivity for diagnosis
- ↑ awareness of 'mimics'
- Addresses: CSF sampling, early and appropriate initiation Aciclovir, imaging



Britton et al. IMJ 2015;45(5):563-76
Britton et al. MJA. 2015;202(11):576-7

Guideline for Australia and New Zealand



Algorithm 2:

'Probable Encephalitis'

- Universal diagnostics and consultation
- Exclusion HSV
- Directed diagnostics based upon <u>risk factors, clinical and radiologic features</u>
- Role of brain biopsy

Britton et al. IMJ 2015;45(5):563-76
Britton et al. MJA. 2015;202(11):576-7

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Australian Government
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CRE Critical Infection

PAEDS
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