Murray Valley encephalitis virus

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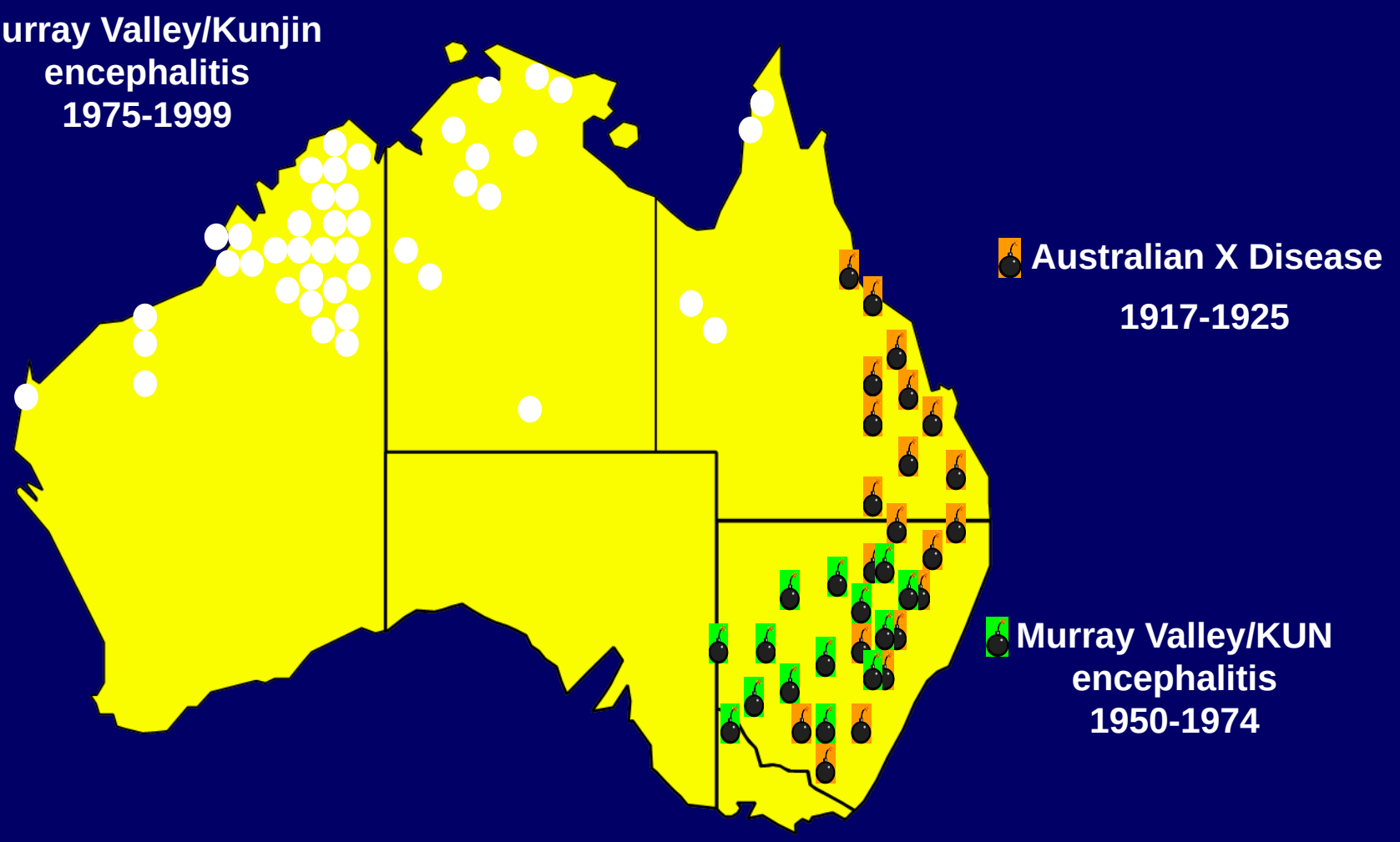
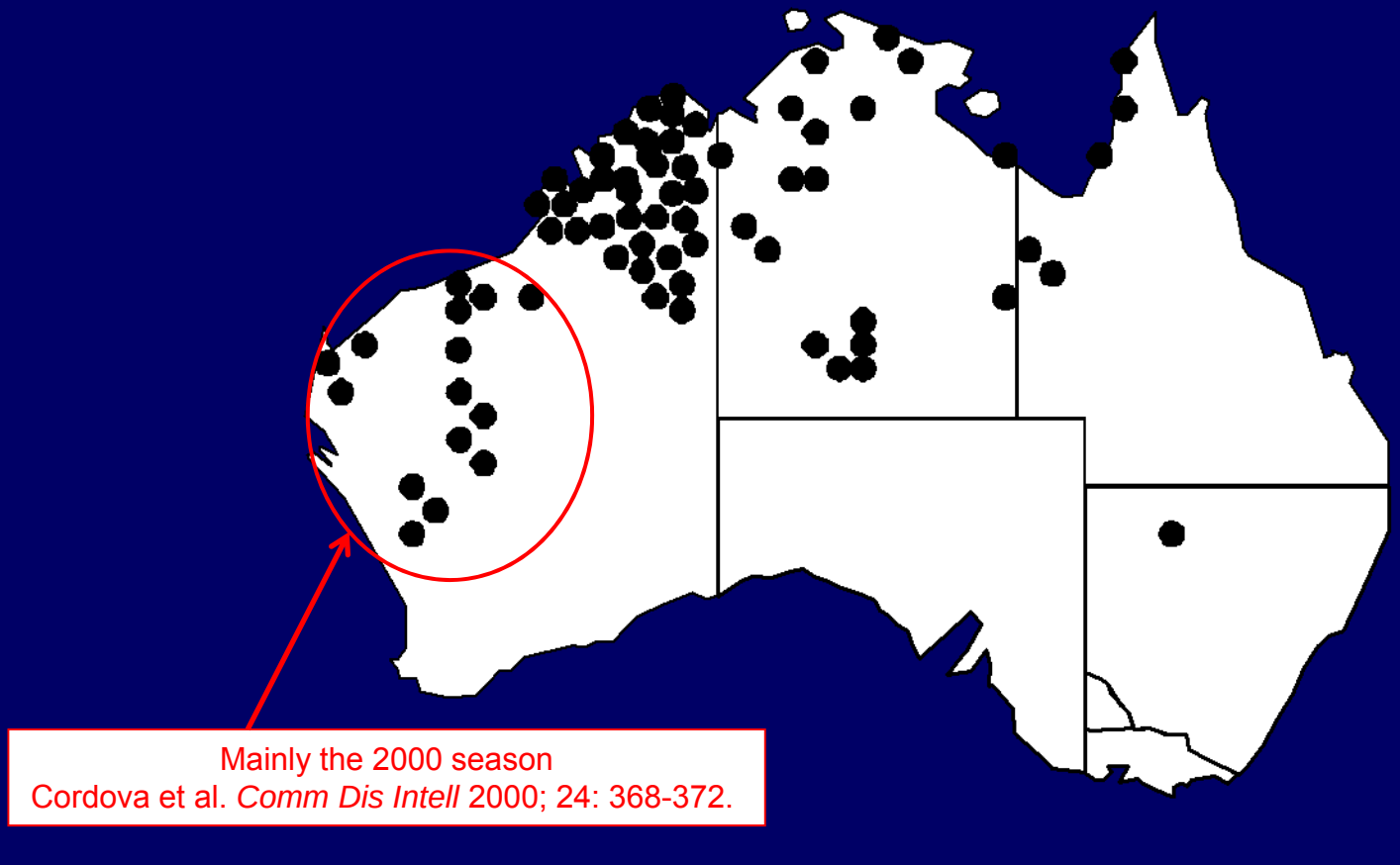
Encephalitic arboviruses

- Alphaviruses:
  - Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, California encephalitis virus
  - Rare cases of encephalitis due to chikungunya virus
- Flaviviruses:
  - Japanese encephalitis virus (JEV), Murray Valley encephalitis virus (MVEV) , West Nile virus (WNV), Kunjin strain of WNV (KUNV/WNV), St Louis encephalitis virus, tick-borne encephalitis virus, louping ill virus, Kyansanur Forest disease virus
- Phleboviruses:
  - Rift Valley fever virus
- Bunyaviruses
  - California encephalitis group

MVE/Kunjin (Australian) Encephalitis 1917 to 1999

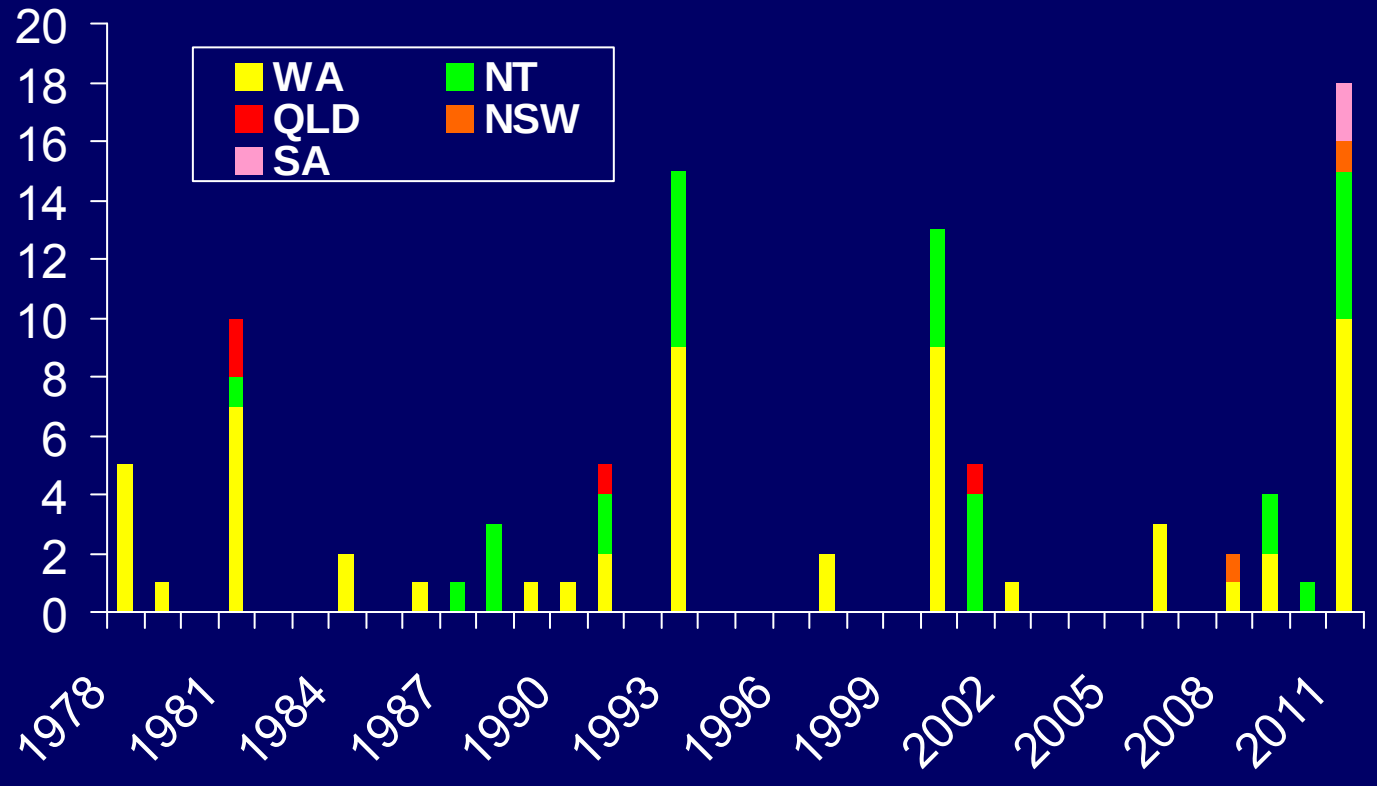


Human MVEV 1975-2010

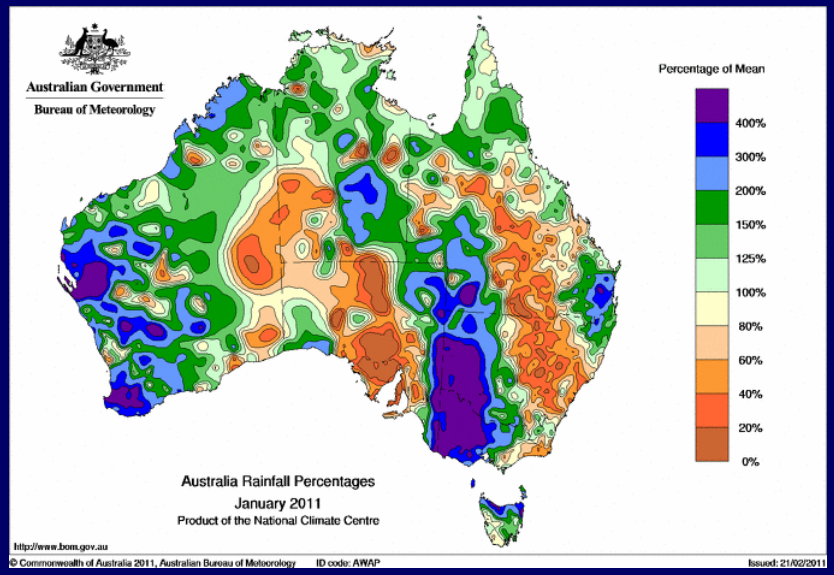


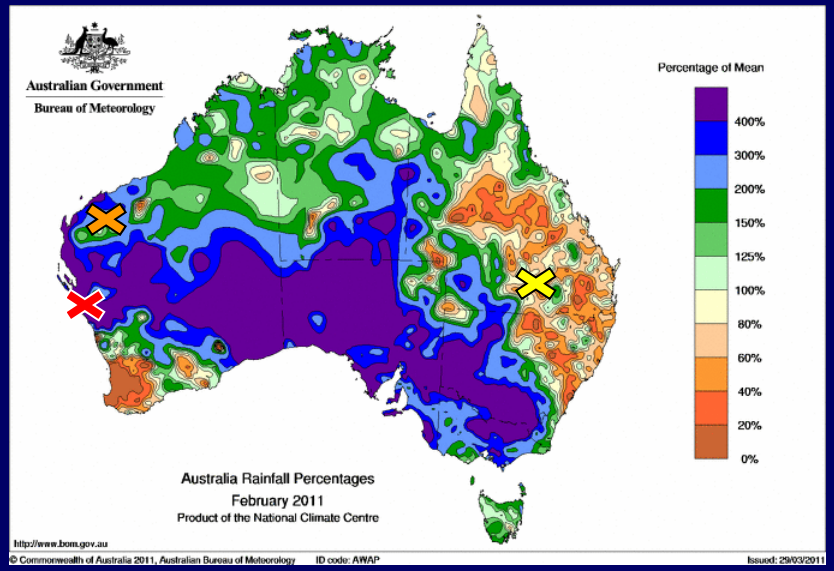
Mainly the 2000 season
Cordova et al. *Comm Dis Intell* 2000; 24: 368-372.

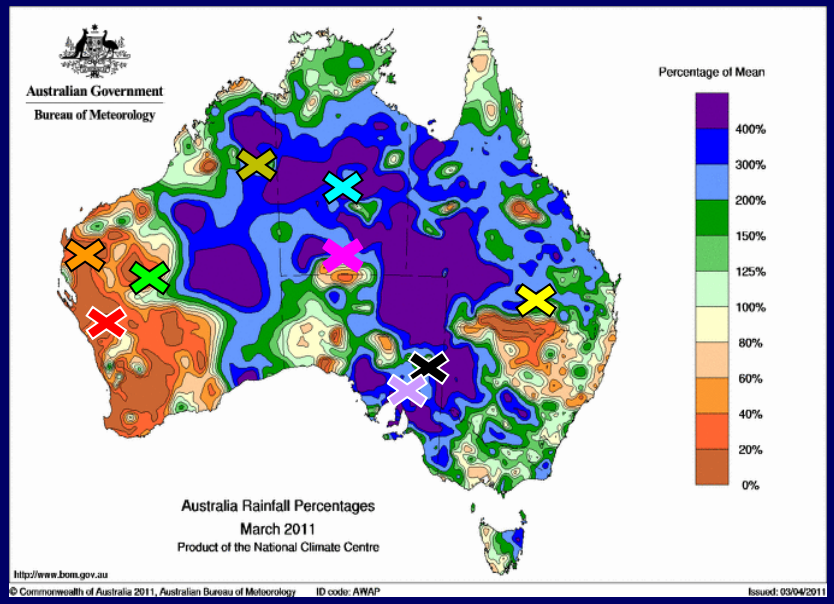
MVEV/KUNV illness in Australia since 1974

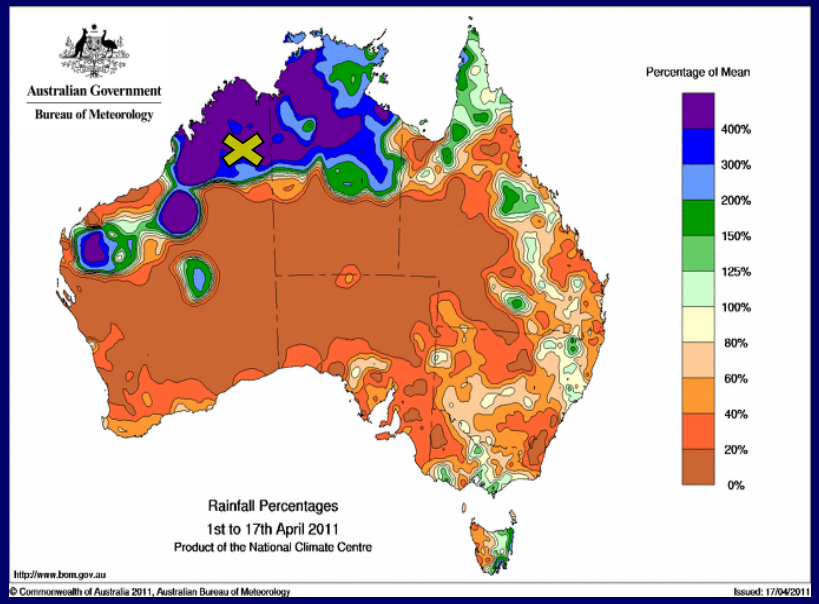


MVEV cases in relation to rainfall data: Note that rainfall may not exactly match groundwater/flooding patterns



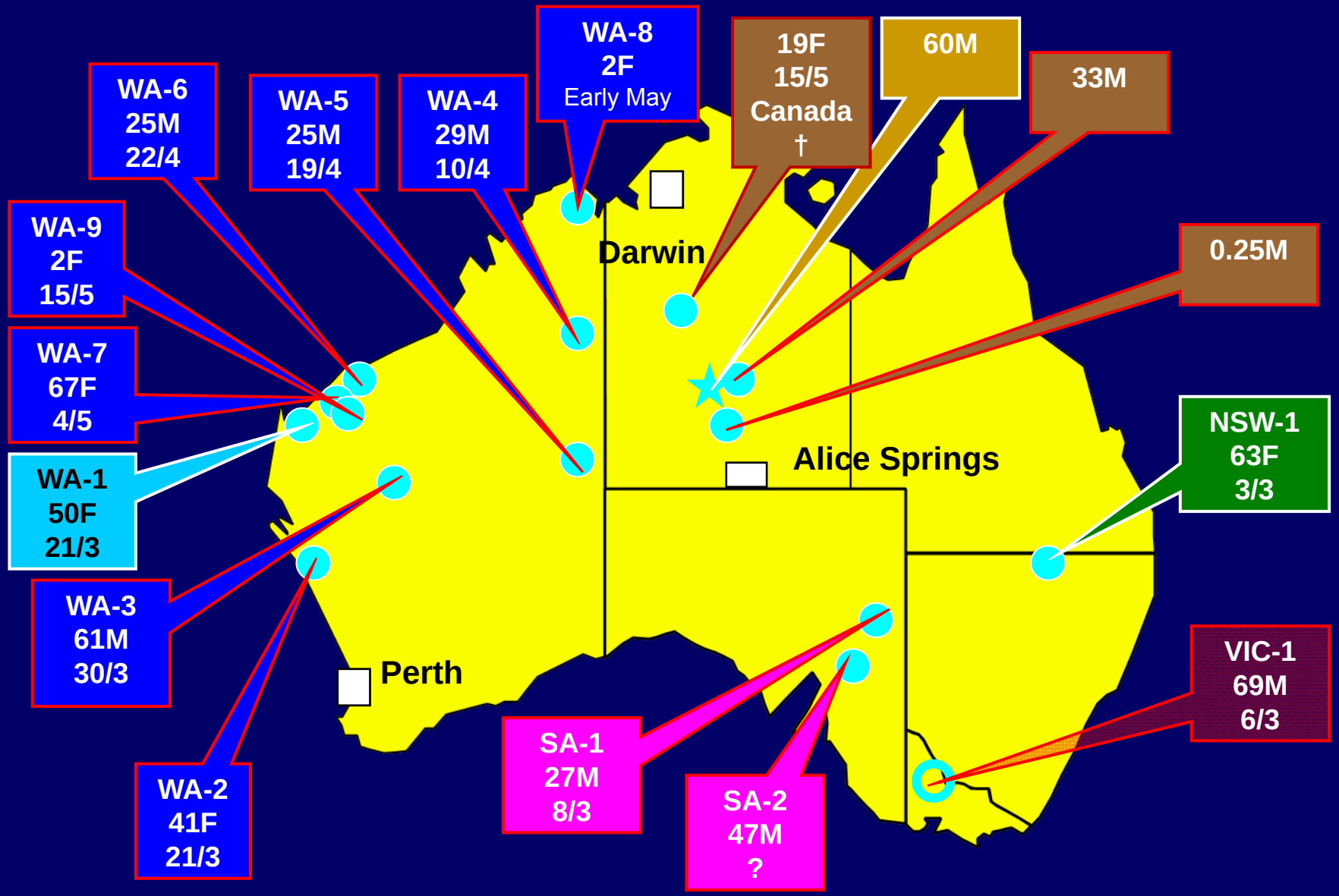






Circle = MVEV. Star = KUNV. Open circle = not lab confirmed. Red outline = encephalitis. White outline non-encephalitic.

Human MVEV & KUNV infections 2011



Flaviviruses: Who gets infected and who gets encephalitis?

- Who gets infected?
  - Populations in enzootic/endemic areas with regular exposure
    - Many infected in childhood or early adulthood
    - Disease in older adults is unusual, e.g JEV in SE Asia, MVEV in the Kimberley
  - People in endemic areas who are not regularly exposed & people in epidemic areas
    - All susceptible, risk depends on exposure
- Who get encephalitis?
  - MVEV 1:200 to 1:1000
  - This may be explained by partial protection due to previous flavivirus exposure in the indigenous population, age related differences, different genetic susceptibility
  - Disease more likely to be under-diagnosed in developing countries

MVEV encephalitis

Maintained in a waterbird-mosquito (*Culex annulirostris)* cycle

Case-to-infection ratio

- 1:1000 to 1:100

Presentation

- May have nonspecific febrile illness +/- headache
- Anorexia, malaise, fever, vomiting
- Adults – headache, altered mental state, occasional fitting
- Children - fitting

Course

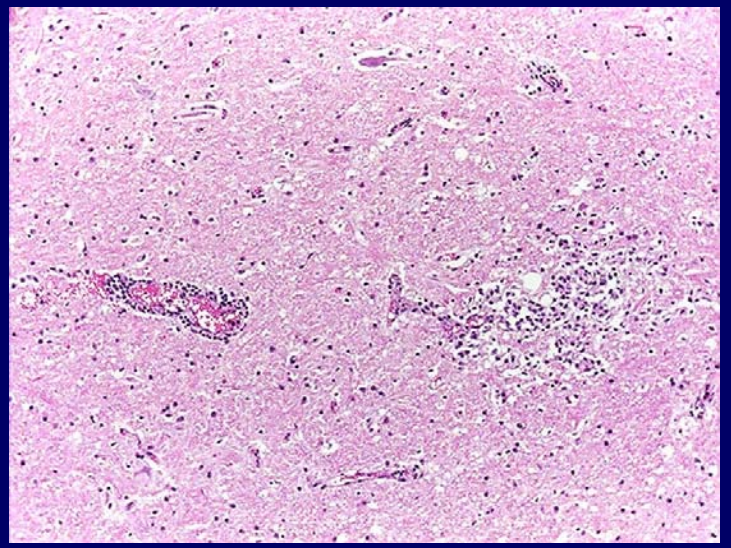
- Variable progression. Involves central cerebral structures, brainstem, spinal cord.
- No specific treatment

Clinical presentations of infection with encephalitic flaviviruses

- Asymptomatic
- Nonspecific febrile illness, usually with headache
- Fever with headache
- Meningitis without encephalitis
- Encephalomyelitis
  - Abortive
  - Classical
  - Acute flaccid paralysis prior to encephalitis (polio-like illness)
    - Up to 1/3 of classical cases also have AFP, but associated with severe neurological diseases
  - Guillain-Barré syndrome (WNV)

What happens when you get it?

- Characteristic features relate to involvement of central cerebral structures including the midbrain, basal ganglia, brainstem and medial temporal lobes
- Cerebellum and upper spinal cord may be affected, particularly the anterior horn cells of the latter.



- Clinical manifestations
  - coma, respiratory failure and flaccid paralysis
  - cranial nerve palsies, tremor, cogwheel rigidity, cerebellar ataxia and upper limb weakness
  - late onset parkinsonism and neuropsychiatric disease

Clinical and radiological predictors of outcome for Murray Valley encephalitis

- Ten cases hospitalised in WA 2008-2011
- All patients acquired infection between March and May, the age range was 2-68 years
- Two children , six males
- Nine infected in WA, one in NSW
- Nine encephalitic, one non-encephalitic
- Investigations
  - All patients developed a raised C-reactive protein, and most developed acute liver injury, neutrophilia and thrombocytosis.
  - MRI

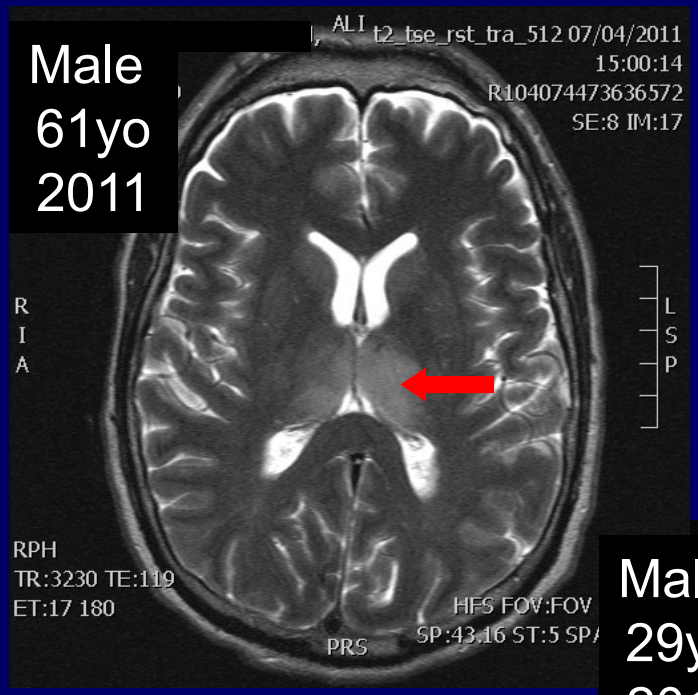
David J Speers, James Flexman, Christopher Blyth, Nirooshan Rooban, Edward Raby, Ganesh Ramaseshan, Susan Benson, and David W Smith. Clinical and radiological predictors of outcome for Murray Valley encephalitis

Clinical and radiological predictors of outcome for Murray Valley encephalitis: MRI findings

- CT scans rarely showed any abnormalities
- MRI findings within 1 week of onset
  - All patients with encephalitis developed cerebral peduncle involvement on early magnetic resonance imaging (MRI).
  - The absence of limbic system MRI hyperintensity, with or without leptomeningeal enhancement, predicted a better neurological outcome
  - Those with widespread abnormalities involving the limbic system and cerebral cortex or the cerebellum had devastating neurological outcomes.
- Later MRI scans showed destruction of the thalamus and basal ganglia, cortex or cerebellum.

David J Speers, James Flexman, Christopher Blyth, Nirooshan Rooban, Edward Raby, Ganesh Ramaseshan, Susan Benson, and David W Smith. Clinical and radiological predictors of outcome for Murray Valley encephalitis

MRI


Male
61yo
2011
ALI t2_tse_rst_tra_512 07/04/2011
15:00:14
R104074473636572
SE:8 IM:17
R
I
A
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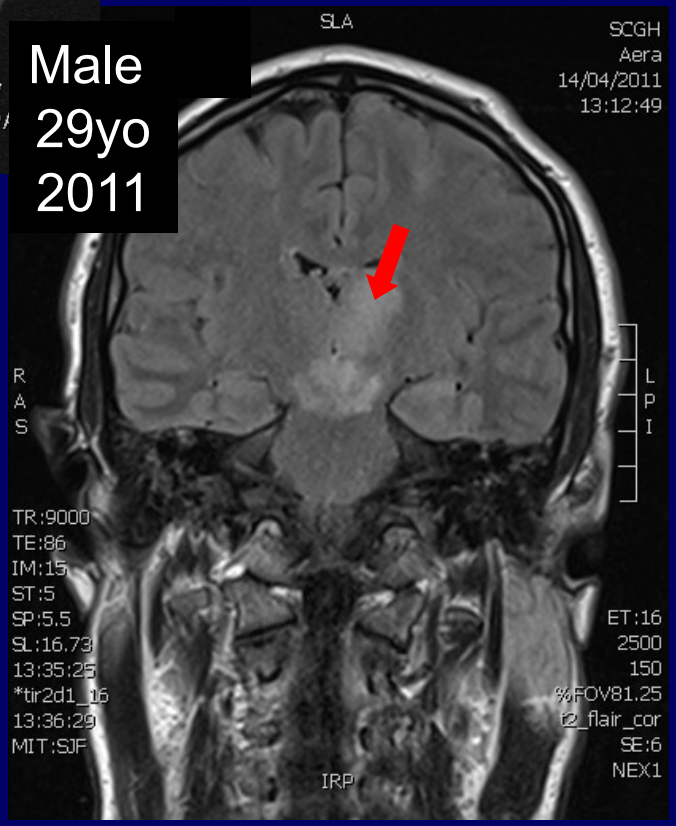
P
RPH
TR:3230 TE:119
ET:17 180
HFS FOV:FOV
PRS


Male
29yo
2011
SLA
SCGH
Aera
14/04/2011
13:12:49
R
A
S
L
P
I
TR:9000
TE:86
IM:15
ST:5
SP:5.5
SL:16.73
13:35:25
*tir2d1_16
13:36:29
MIT:SJF
ET:16
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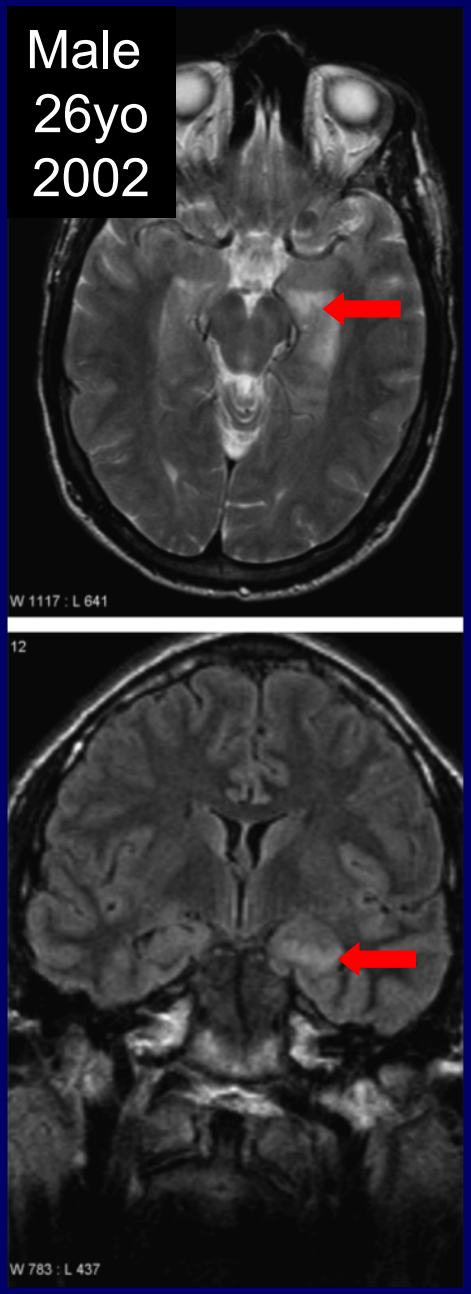
150
%FOV81.25
t2_flair_cor
SE:6
NEX1
IRP

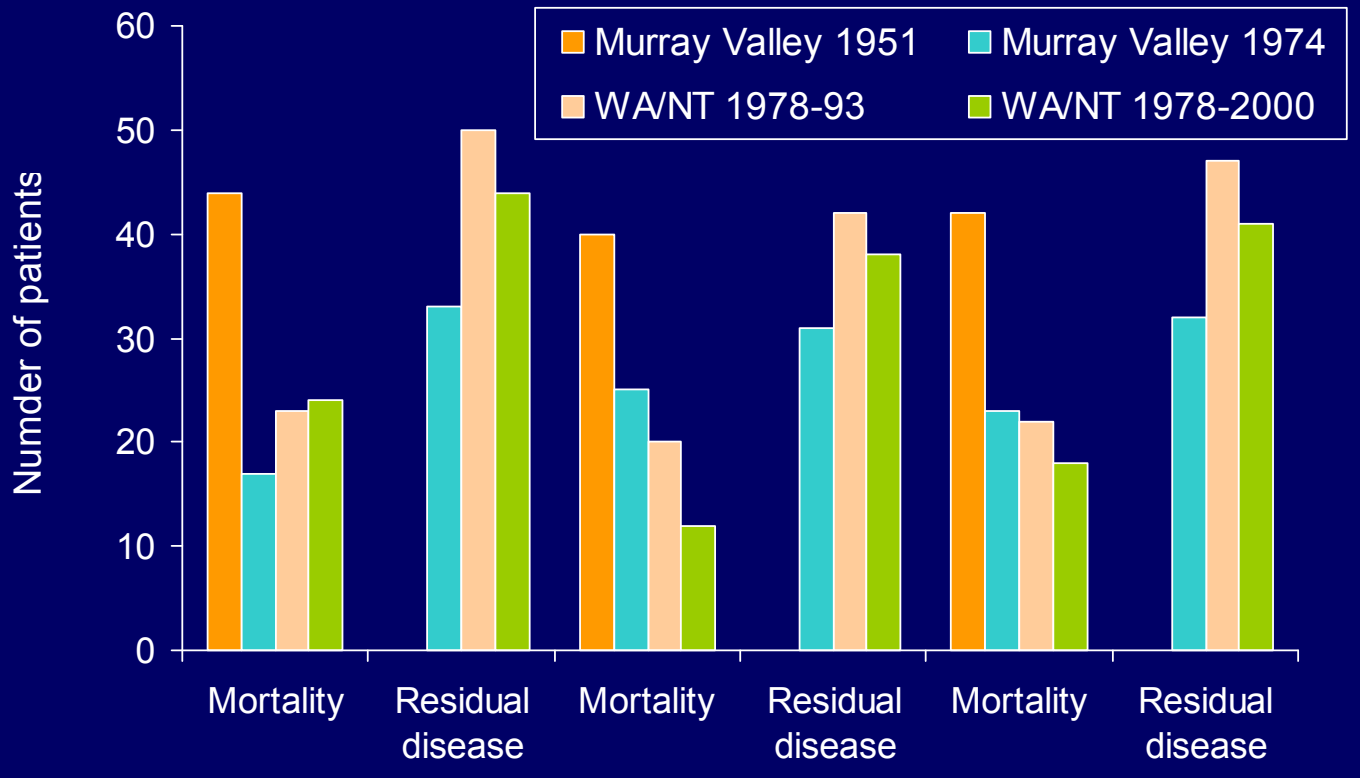

Male
26yo
2002
W 1117 : L 641
12
W 783 : L 437

Outcome of MVE encephalitis: WA/NT 1978-2011

	Number	*Mortality*	*Sequelae*	*Normal*
Adults	**38**	**6 (16%)**	**17 (45%)**	**15 (39%)**
Children	**27**	**6 (22%)**	**12 (44%)**	**9 (34%)**

- **Worst outcomes in adults over 50 years and children under 2 years**
- **Little evidence of improvement in survival or neurological sequelae since 1974**
- **Improving survival may increase number with severe neurological sequelae**

MVEV encephalitis outcomes

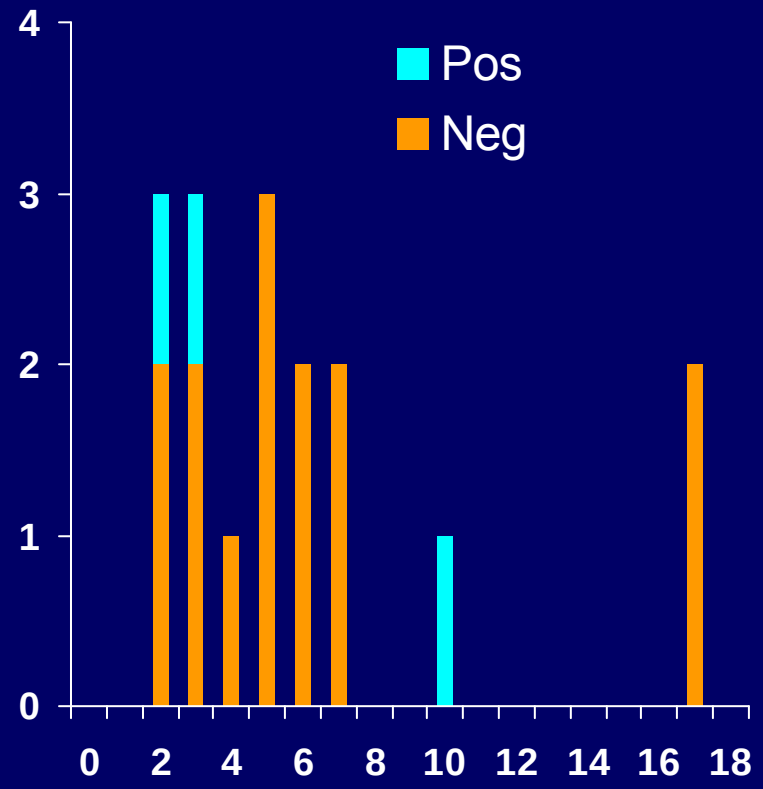


Diagnosing flavivirus encephalitis

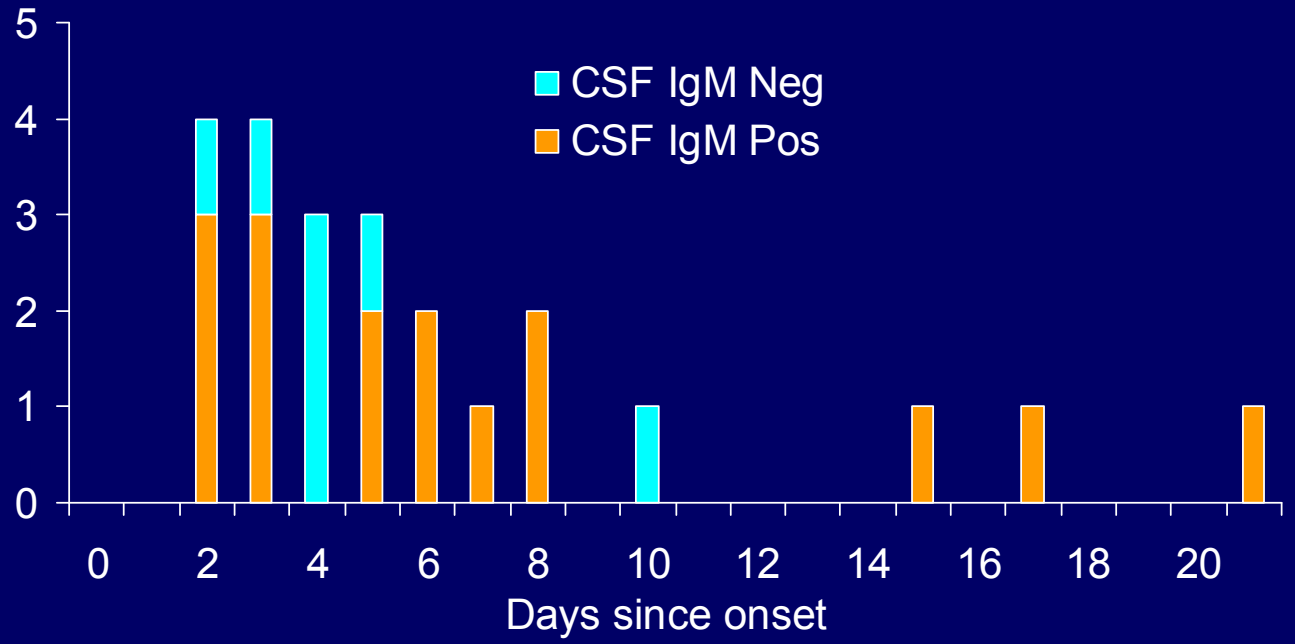
- CSF shows variable pleocytosis and variable proportion of neutrophils. Usually mildly elevated protein, normal glucose.
- Detection of virus by culture is rare in premortem samples (CSF or blood)
- Detection of virus by PCR is uncommon in premortem samples (CSF or blood) for most flaviviruses
- Detection of IgM in CSF is helpful and diagnostic of flavivirus encephalitis, but only found in ~75%.
- Detection of IgM in serum may be helpful but does not necessarily mean recent infection and may not indicate which flavivirus
- Rising levels of IgG between acute and convalescent samples is very helpful in confirming recent flavivirus infection, but may not tell you which one it is.
  - Species specific serology should be performed – neutrlaistion or epitope-blocking EIA
- Patients with second flavivirus infections, e.g. MVEV infection in someone with past Kunjin infection
  - IgM may be absent
  - Early IgG response may be directed at the previously infecting flavivirus
- REMEMBER
  - Serological diagnosis can be tricky
  - You never have enough CSF!

PCR for MVEV in CSF

- Target is the envelope protein sequence
- Nested in-house (plus tandem nested real-time 2008 onwards)
- 20 samples tested from 17 patients with known date of onset of illness
  - 3 positive
- One additional patient had positive PCR on postmortem brain tissues



MVE encephalitis 2000-2011
CSF IgM by IFA



18 patients, 23 samples

Overall, 13/18 (72%) of patients had IgM detectable in CSF

Treatment of flavivirus encephalitis

- Supportive care the only current recommendation for treatment
- Corticosteroids
  - Dexamethasone - no benefit against JEV encephalitis in double-blind placebo-controlled trial
  - Glucocorticoids increase WNV viraemia in dogs
  - Isoquinolone compounds are effective in vitro
- Interferon
  - Recombinant interferon-α promising in open trial, but no benefit for JEV encephalitis in a placebo controlled double blind trial
- Ribavirin
  - Shown to inhibit WNV in vitro , but no benefit in WNV patients treated during 2000 outbreak in Israel or for JEV encephalitis in a placebo controlled trial in India.
  - Does not effectively cross the blood–brain barrier
- Intravenous immunoglobulin (IVIG) therapy
  - Monoclonal antibodies are apparently effective in animal models
  - Case reports and mouse studies suggest IVIG containing high titres of anti-WNV antibodies improves WNV encephalitis outcomes, particularly in immunocompromised patients
  - Phase I/II clinical trials of WNV-specific IVIG have recently been completed in the US, but results are yet to be reported.

Knox J *et* al. Med J Aust 2012; 196 (5): 322-326.

Prevention

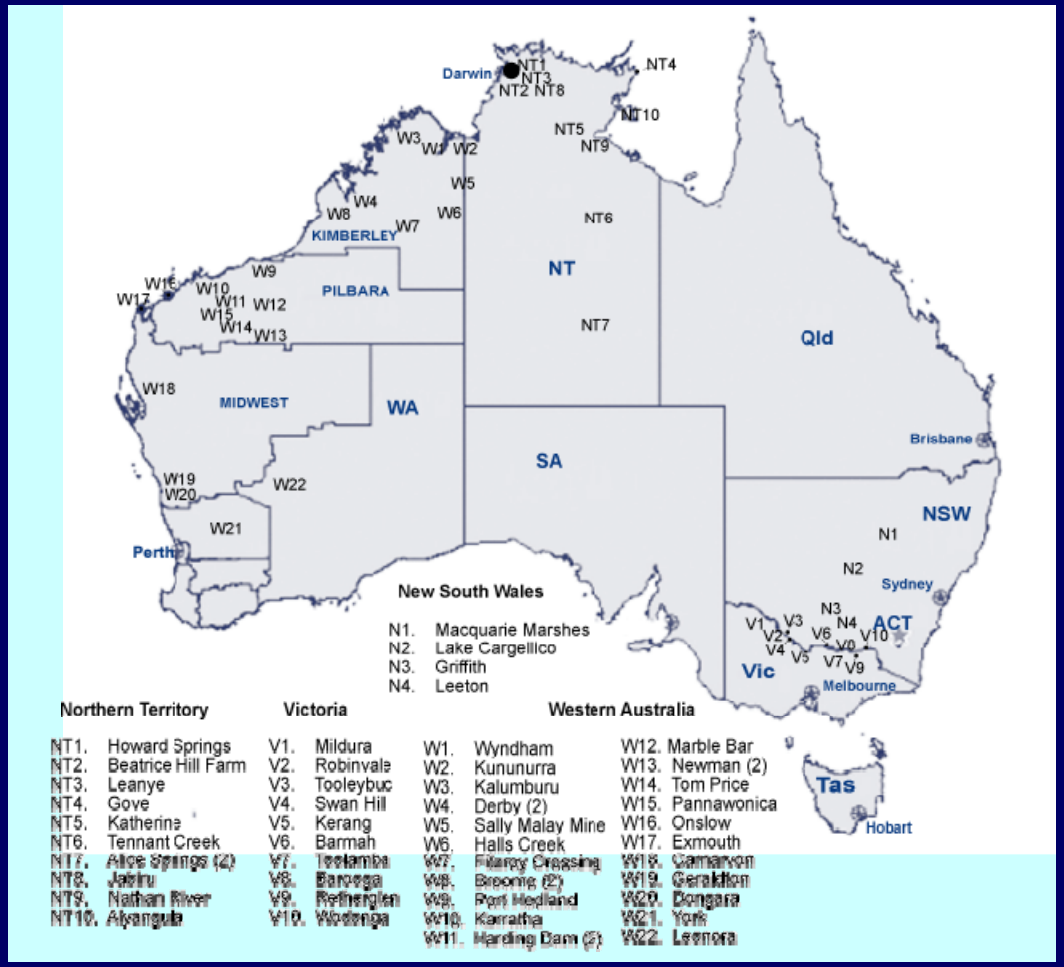
- Risk monitoring and public warnings
  - Travel to areas with activity
  - Mosquito avoidance
- Vaccine?

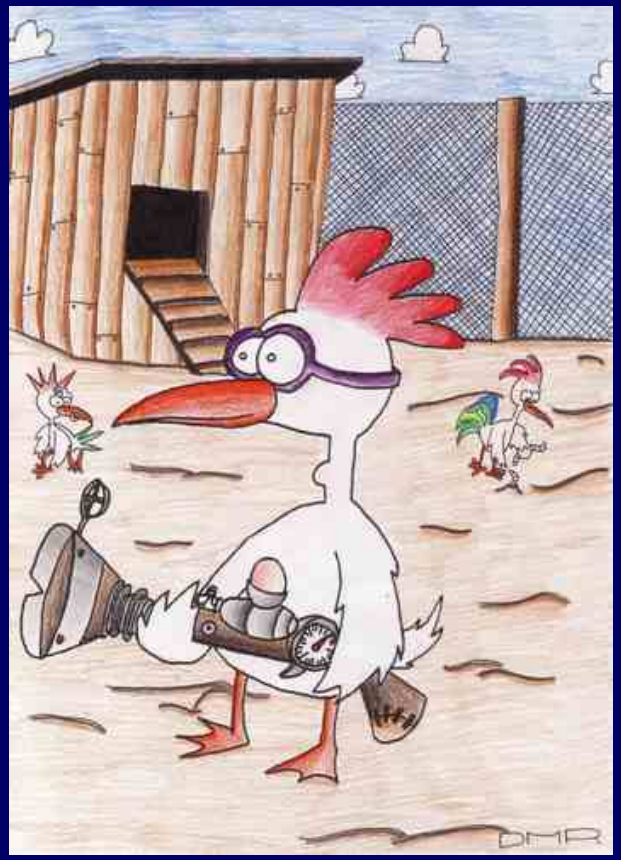
What's needed to get human infections?

Risk condition	Monitoring the risk
Weather conditions - Needs to have heavy rains and flooding, and warmth	**Meteorological data, satellite data**
Vectors: Needs mosquitoes – *Culex annulirostris*	**Mosquito trapping***
MVEV present in the mosquitoes	**Testing trapped mosquitoes***
Amplifying hosts: Mainly water birds that have not been previously exposed	**Nil**
Infected mosquitoes biting humans	**Sentinel chicken monitoring**
People getting exposed to infected mosquitoes: Possible dose effect – ? need lots of bites to get encephalitis	**Clinical cases**

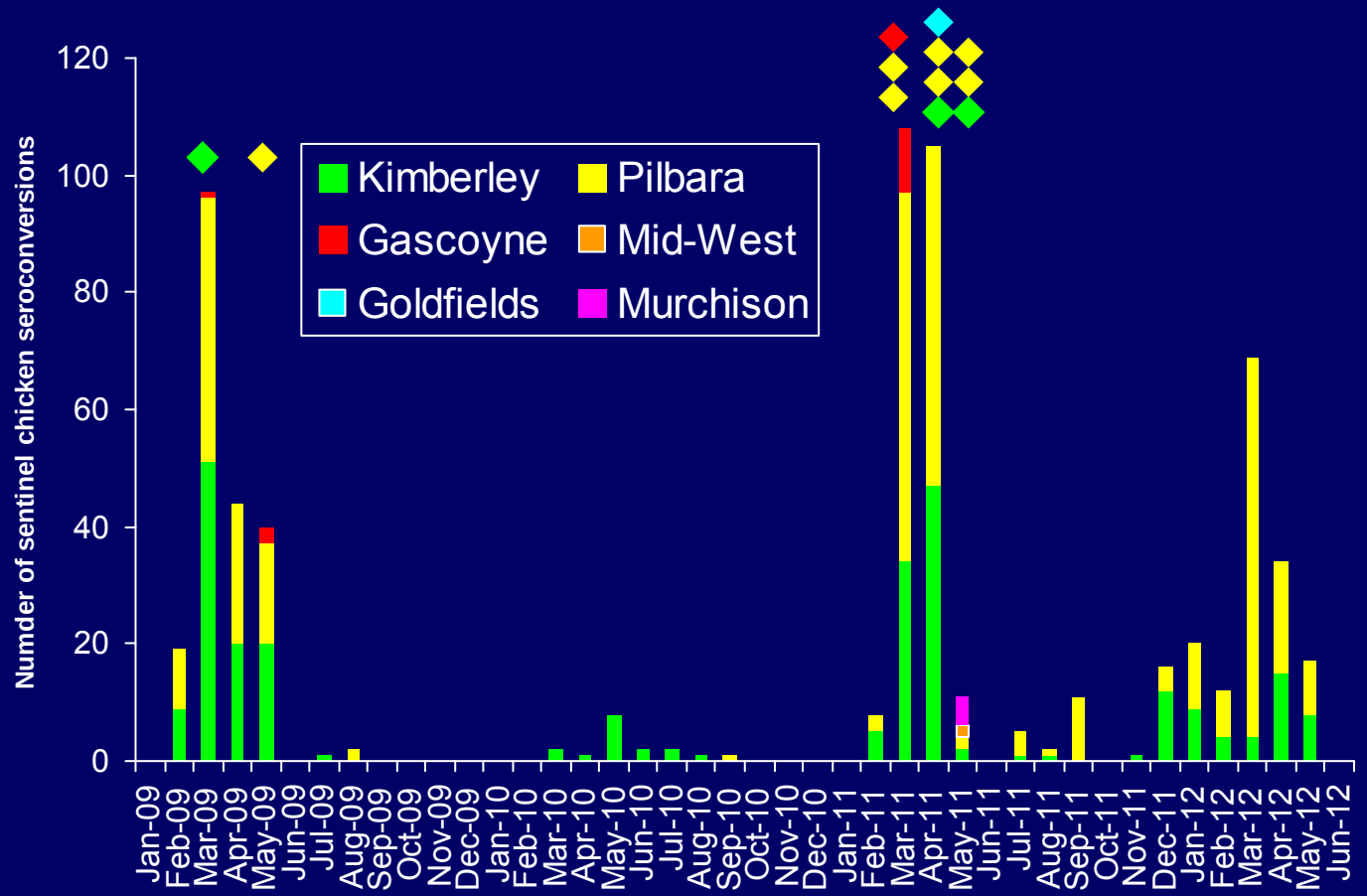
* Often not feasible during the wet season due to limited access

Sentinel chickens





Sentinel chicken MVEV seroconversions and human cases Jan 2009- May 2012



Data from Arbovirus Surveillance and Research Laboratory, University of Western Australia

If people act on warnings, could they avoid infection?

- 50 yo female – regular mosquito exposure in evenings
- 41 yo female – regular night fishing
- 61 yo male – camping by roadside
- 29 yo male – outdoor job
- 25 yo male – regular evening outdoor activities
- 25 yo male – fishing and camping
- 67y yo female – camping at beach and other locations
- 2 yo female – many mosquito bites

MVEV vaccination

- No specific MVEV vaccine available
- Current flavivirus vaccines: JEV, TBEV, (WNV), (DENV)
- JEV most closely related to MVEV
  - Inactivated JEV vaccines- enhance MVEV infection in mouse model
  - Chimeric vaccine protects against JEV in mice – would it do the same in humans?

Acknowledgements

WA
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