

ADULT IMMUNISATION FORUM

2023

This event will start at 8:30am AWST

22 JUNE 2023

8:30AM–5:00PM AWST



IMMUNISATION
COALITION

SESSION 2



Annaleise Howard-Jones

Japanese Encephalitis and Murray Valley Encephalitis



Peter Richmond

RSV and Pregnancy



Chris Blyth

Protecting the Future – What's New in Antenatal Vaccination

Annaleise Howard-Jones

Japanese Encephalitis Virus & Murray Valley Encephalitis Virus:

(Re)-Emergence of Flaviviruses in Australia



NSW Health Pathology-ICPMR

22nd June 2023

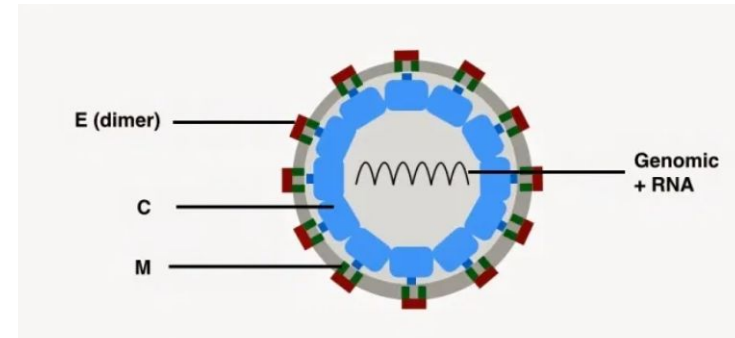
Acknowledgement of Country

We acknowledge the Traditional Owners of the lands on which we meet today - the Darug People of the Darug Nation - and pay our respects to their Elders past, present and emerging.

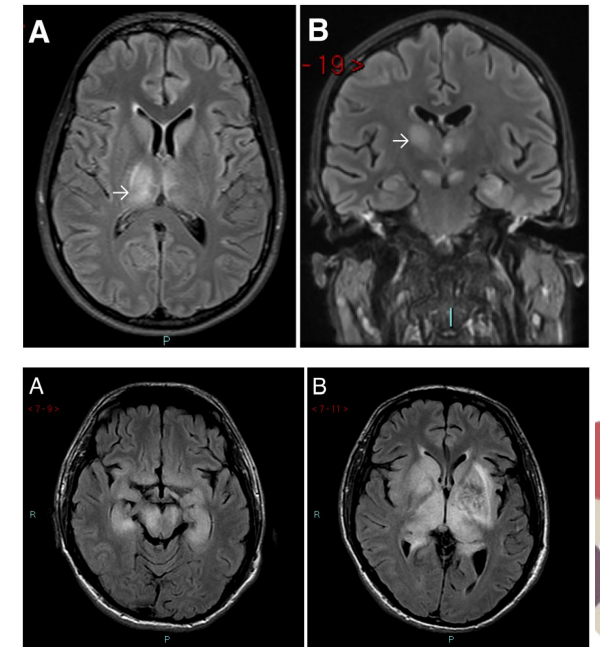
Flaviviruses: Overview

Neurotropic RNA virus - enveloped ss positive sense
Flaviviridae family:

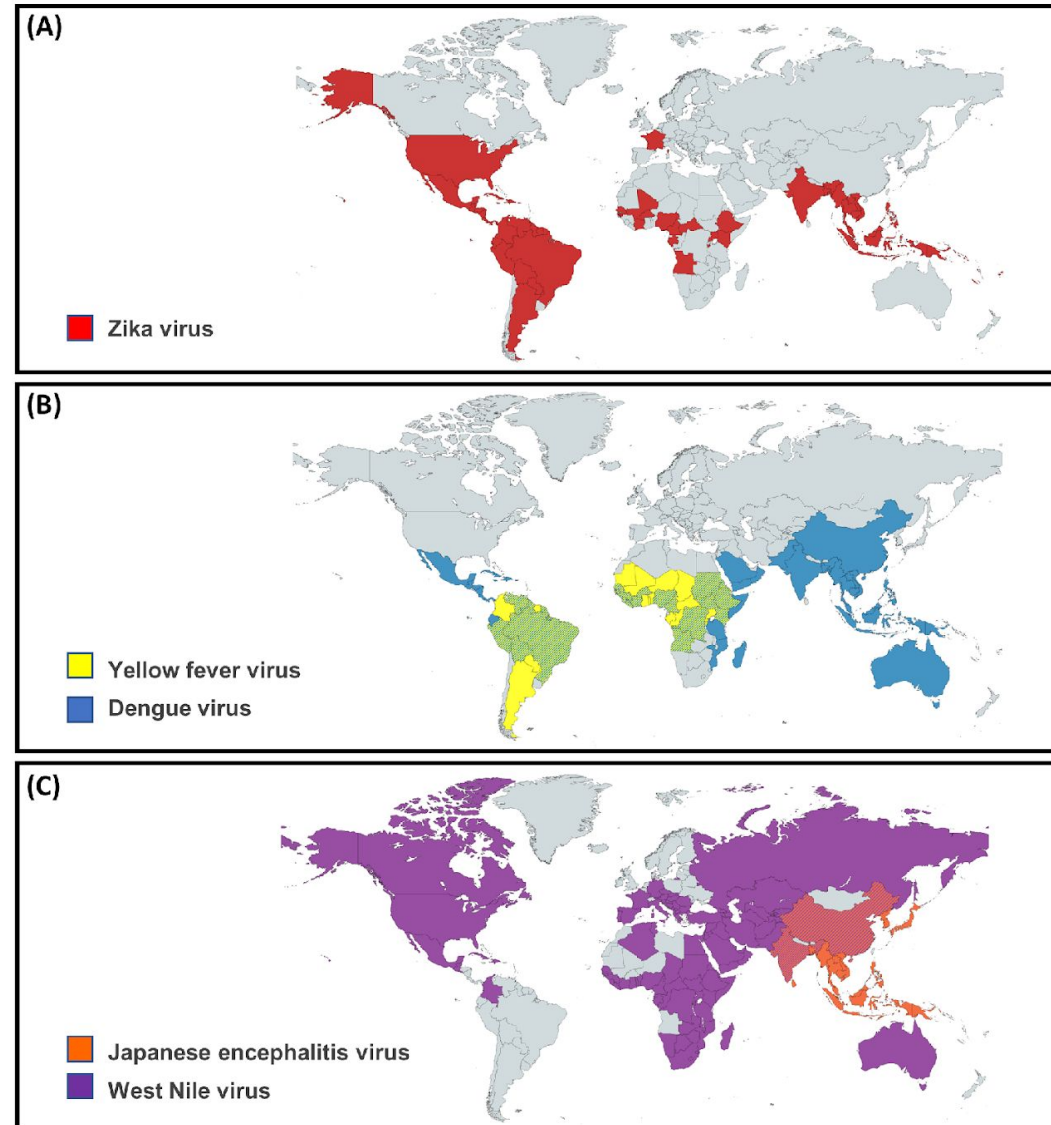
- Japanese encephalitis virus
 - Murray Valley encephalitis virus
 - West Nile virus (including **Kunjin strain**)
 - St Louis encephalitis virus
 - Tick-borne encephalitis virus
 - Louping ill virus
-
- Zika virus
 - Dengue
 - Yellow fever virus



Highly
neurotropic

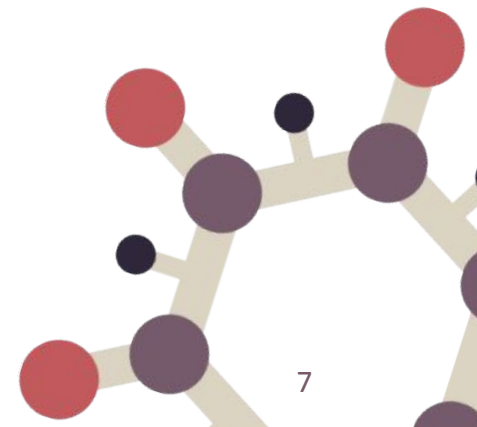


Geographic Distribution of Flaviviruses

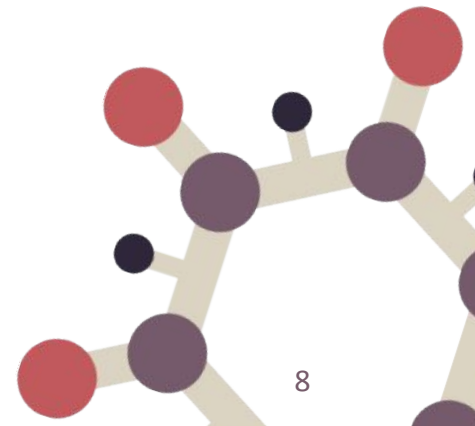
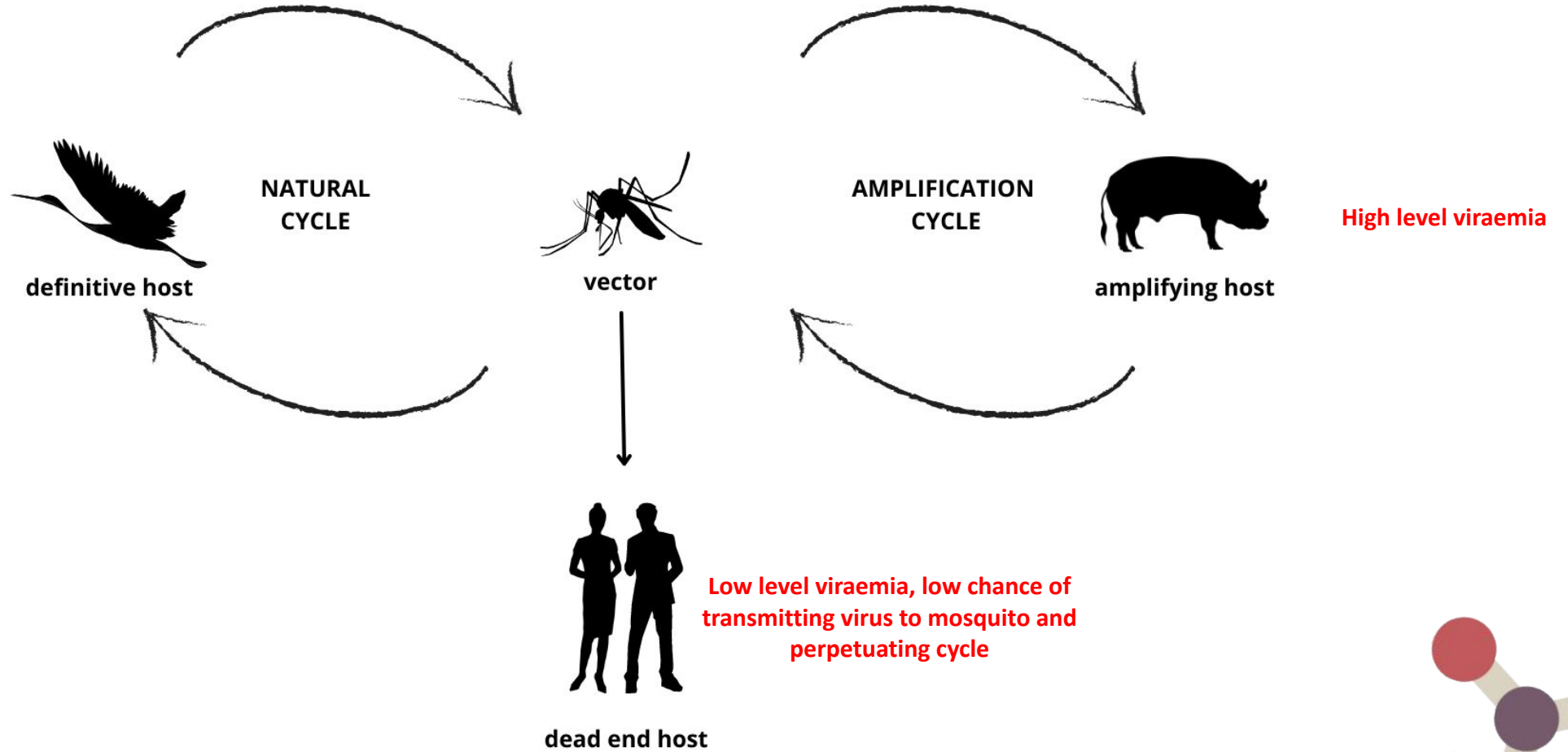


The Tale of Two Seasons

2022: Japanese Encephalitis Virus



JEV Lifecycle



JEV: Clinical Presentation

Most common cause of viral encephalitis in SE Asia & Western Pacific

Incubation period: 5-15 days

Wide clinical spectrum:

- Asymptomatic infection
- Non-encephalitic illness (fever, myalgia, headache common)
- Encephalitis (approx 1 per 250 cases)
- Overall case fatality: 0.3-25%

Encephalitic disease, though rare, carries high morbidity & mortality

- Case fatality: 5-50%
- Brain stem dysfunction, 'locked-in syndrome', long-term seizure disorders in 40%

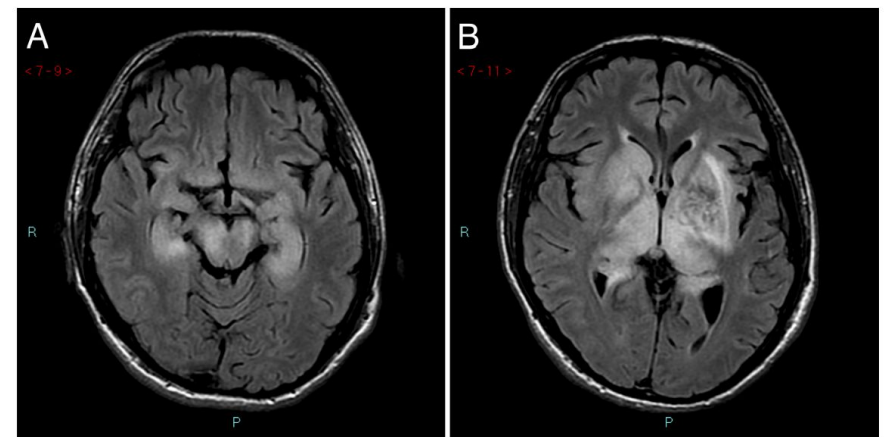
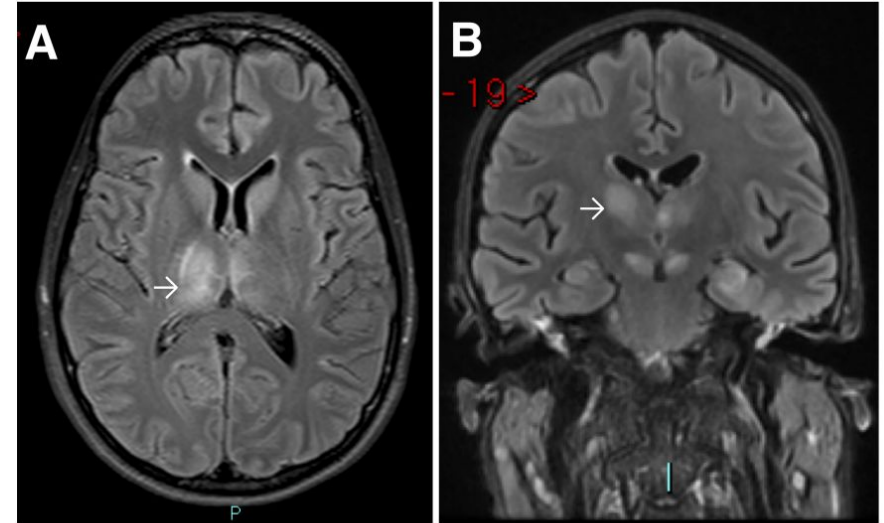
JEV: Clinical Presentation

CSF findings

- Pleocytosis common (not universal)
- Lymphocyte predominance
- Raised protein

Neuroimaging (MRI optimal)

- Focal lesions in thalamus (74%) > basal ganglia, brainstem, medial temporal lobe
- Meningeal enhancement (13%)



JEV: Australian Outbreak Timeline

25th February 2022

DPI reported JEV detection in commercial piggeries across NSW, VIC, Queensland (later in SA)

- Confirmed genotype 4
- Fetal loss & congenital anomalies in piglets
- Huge commercial implications

3rd March 2022

First human case detection in NSW (fatal), post-mortem Dx

4th March 2022

JEV declared Communicable Disease of National Significance by Acting CHO

7th March 2022

Establishment of multi-modal diagnostic capacity for JEV

- Molecular assay introduction & validation (RT-PCR)
- Serological assay development
- Viral culture methodologies

Diagnosis of Flavivirus Infection

Detailed clinical history

- Clinical symptoms & timing
- Exposure history:
 - Residence
 - Regional / international travel
 - Timing of contact
 - Recreational activities & occupational risk
 - Mosquito contact & avoidance behaviours
- Vaccination history (for all flaviviruses)

Physical examination (including neurological) +/- neuroimaging

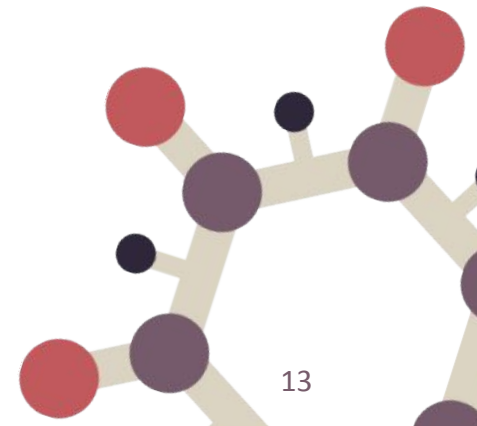
Diagnosis of Flavivirus Infection

Suitable samples for diagnosis:

- Blood, urine, CSF, tissue for **PCR**
 - Sampling early in illness has highest yield
 - Detection of flavivirus-specific RNA is diagnostic (highly specific)

AND

- **Serology** – minimum two serum samples
 - Acute, and
 - Convalescent (+2-4 weeks from symptom onset)
 - Diagnosis can be made on basis of :
 - Presence of IgM specific for that flavivirus; and/or
 - Significant (4x or greater) rise in IgG or total Ab titre
 - Must also test for other possible flaviviruses due to cross-reactivity (shared epitopes)



Diagnosis of Flavivirus Infection

Detailed history of symptoms & exposures

+

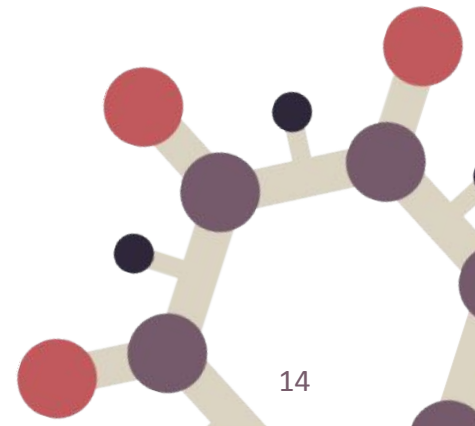
Knowledge of local epidemiology



Bespoke panel of flaviviruses warranting testing

In rural Australia: MVEV, JEV & Kunjin

International travel: also test for dengue, YFV, Zika, or other
(dependent on specifics of travel)



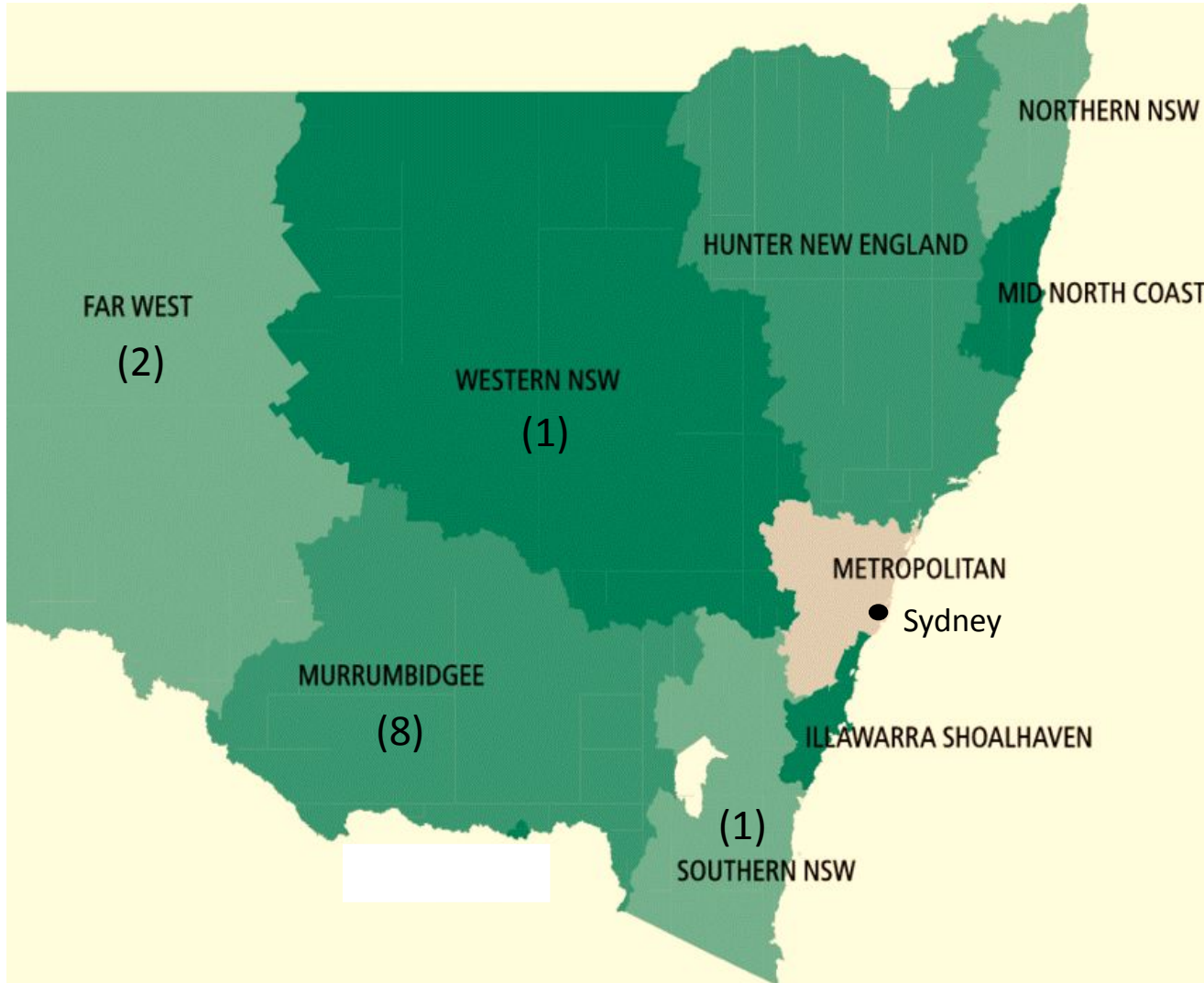
NSW Case Detections

n=12 (to 31st May 2022)

Case #	CSF JEV IgM IFA	Serum JEV IgM IFA	Serum JEV IgG (interval)	JEV RT-PCR	mNGS	Confirmed / Probable JE
1	detected	detected	>8x titre rise (7 days)	detected (brain tissue & CSF)	JEV sequence detected (brain tissue)	confirmed
2	not detected	not detected	not detected	not detected (CSF)	-	confirmed
3	not detected	detected	not detected	not detected	-	confirmed
4	-	detected	not detected	not detected	-	confirmed
5	-	detected	not detected	not detected	-	confirmed
6	-	detected	not detected	not detected	-	confirmed
7	-	detected	not detected	not detected	-	confirmed
8	-	detected	>8x titre rise (20 days)	not detected	-	confirmed
9	-	detected	>4x titre rise (19 days)	-	-	confirmed
10	-	detected	detected; no convalescent serum available	-	-	confirmed
11	-	detected	detected; no convalescent serum available	-	-	confirmed
12	-	detected	>8x titre rise (41 days)	-	-	confirmed

Highest diagnostic yield is for serology
Targeted molecular testing can be high yield
- e.g. brain tissue in unexplained encephalitis

NSW Case Detections



n = 12

Median age: 49.7 years

IQR 30.4 to 65.9 years

Range 10.1 to 73.7 years

Male:Female ratio 2.0

1 paediatric case – diagnosed by serology

First 3 months of outbreak:

0.15 JE cases per 100,000 population (NSW)

Prevalence of non-encephalitic disease unknown

Historical JEV Look-Back (2021)

Historical lookback of CSFs from across NSW

- 145 CSF samples received from 127 patients with unexplained encephalitis
- Date range: 1 October 2021 - 3 March 2022
- **No detections of JEV (IgM and/or PCR)**

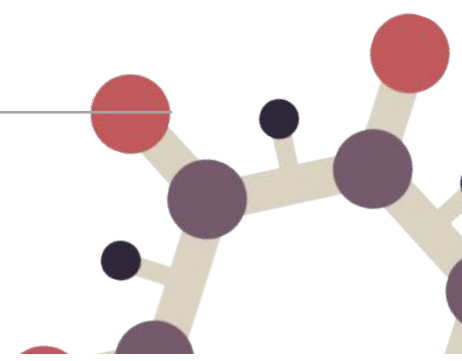
Conclusion:

- **No evidence of human JE cases in six months preceding 2022 outbreak**
[Caveat: limited sampling]

National JE Cases: to 24 February 2023

	Confirmed	Probable	Fatalities
NSW	14	-	2
Vic	11	3	1
SA	6	4	2
NT	2		1
QLD	2	3	1
Total	35	10	7

Case fatality rate: 20%
(encephalitic disease)



JEV Vaccination Strategy (ATAGI)

On 24 March 2022, JE vaccine recommendations were expanded

- Included all people over 2 months of age in high-risk geographic settings

Each state and territory health department was responsible for:

- Defining eligibility criteria for people in high-risk settings, and
- Distribution of vaccines

Available JEV Vaccines in Australia

Vaccine type	Vaccine Viral strain	Population	Schedule/route	Booster (if ongoing risk)
Inactivated	JEspect (CSL/ Valneva aka Ixiaro)	≥2 months to <3 years	0.25 mL IMI 2 doses (28 days apart)	No recommendation
		≥3 to <18 years	0.5 mL IMI 2 doses (28 days apart)	
		≥18 years	0.5 mL IMI 2 doses (28 days apart) *accelerated primary course 7 days apart if they are at imminent risk of exposure	1–2 years after primary dose if ongoing risk of JE virus exposure
Live chimeric (attenuated)	Imojev (Sanofi; aka ChimeriVax)	≥9 months to <18 years	1 dose SCI	1–2 years after primary dose if ongoing risk of JE virus exposure
		Not for immunocompromised, pregnant or breastfeeding		
		≥18 years	1 dose SCI	Not required
		Not for immunocompromised, pregnant or breastfeeding		

Vaccination Delivery Across Australia

In 2022, at least 85,930 people completed a course of a JEV vaccine

- Majority received Imojev (live attenuated)
 - Suitable for people aged ≥ 9 months where there are no contraindications to its use
 - Contraindicated in pregnant women and immunocompromised people
 - Not licensed for use in children < 9 months of age
- JEspect (inactivated vaccine) recommended for:
 - Pregnant women,
 - Children aged 2 months to < 9 months, and
 - Immunocompromised individuals

Unanswered Questions

Origin of 2022 outbreak

Potential endemicity in Australia

Ongoing disease burden of flaviviruses in Australia

- Prevalence of non-encephalitic & asymptomatic disease
- Seasonality in SE Australia vs Northern Australia
- Role of ongoing climate change pressures

Vigilance for other emergent pathogens at human-animal interface

Increased Surveillance Activities

- Mosquito trapping
 - characterising species, infection rates, viruses
- Virus detection and characterisation from humans, mosquitos, animals
 - culture, genomics, PCR
- Serological testing programs
 - humans, chickens, birds, pigs

Human JEV Serosurvey (NCIRS)

June-July 2022

NSW Health

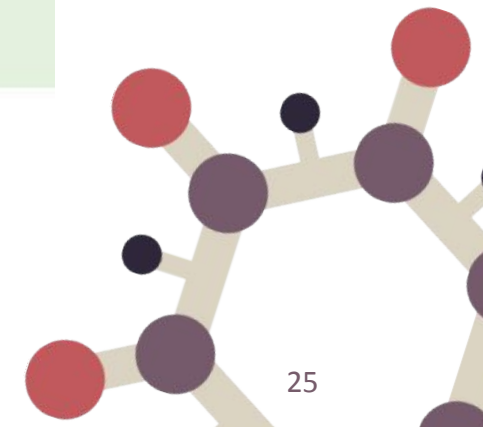
Report

Summary of NSW Japanese encephalitis virus serosurvey results



Report released 12 January 2023

<https://www.health.nsw.gov.au/environment/pests/vector/Documents/jev-serosurvey-report.pdf>



JEV NSW Serosurvey (NCIRS), June-July 2022



1,048 people gave a blood sample & completed a questionnaire



1 in 11 participants had evidence of JEV infection



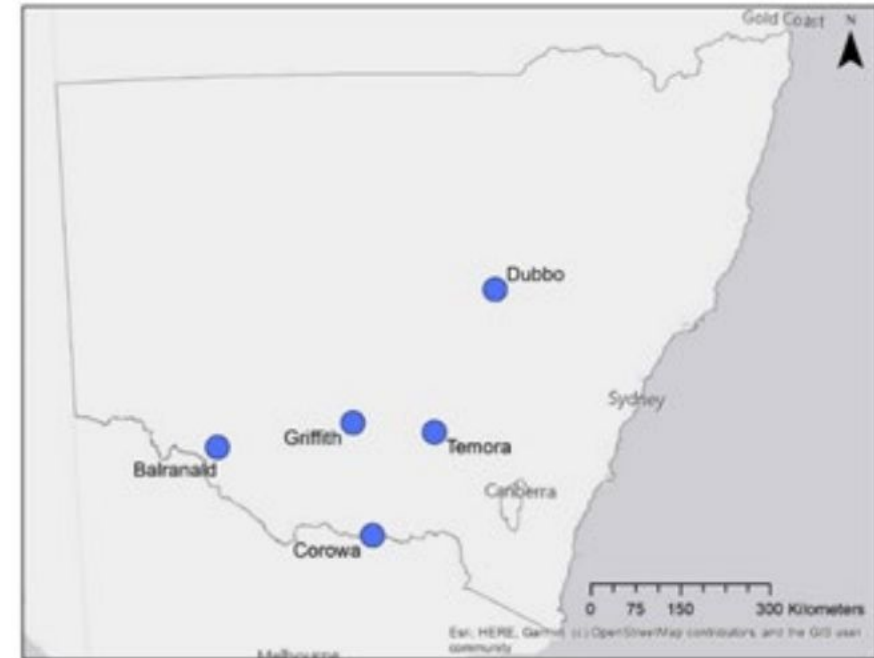
Participants aged between **20 – 87** years had evidence of JEV infection



More participants **> 50** years had evidence of JEV infection



Participants from all **5** towns had evidence of JEV infection



JEV IgG detected in **8.7%** (80/917) participants

JEV NSW Serosurvey (NCIRS), June-July 2022

Conclusions

- JEV was prevalent in these rural areas of NSW and may have affected a large number of people.
- Messaging helpful to encourage uptake of vaccine & mosquito-avoidance behaviours



1,048 people gave a blood sample & completed a questionnaire



1 in 11 participants had evidence of JEV infection



Participants aged between **20 – 87** years had evidence of JEV infection



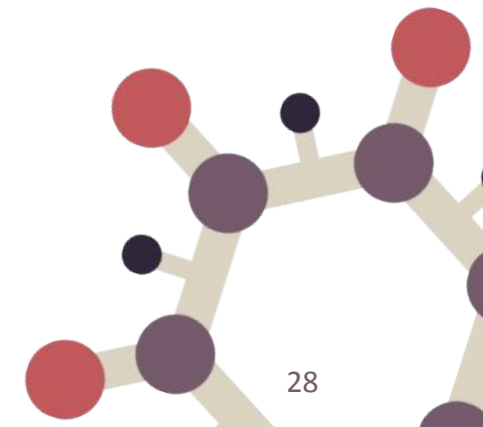
More participants **> 50** years had evidence of JEV infection



Participants from all **5** towns had evidence of JEV infection

The Tale of Two Seasons

2023: Re-Emergence of MVEV

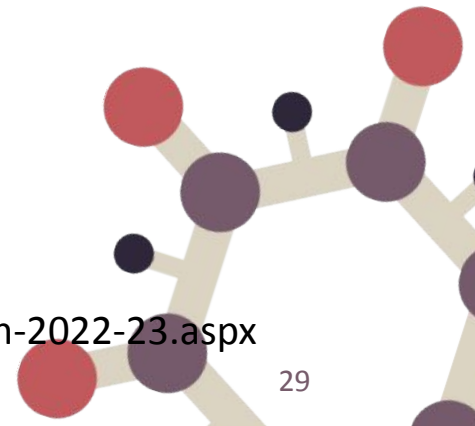


Mosquito / Chicken Arbovirus Surveillance – 2022-2023

Mosquito Monitoring 2022-2023

Weekly Update: Week ending 22 April 2023

(Report Number 27)



Sentinel Chicken Seroconversions - 2023

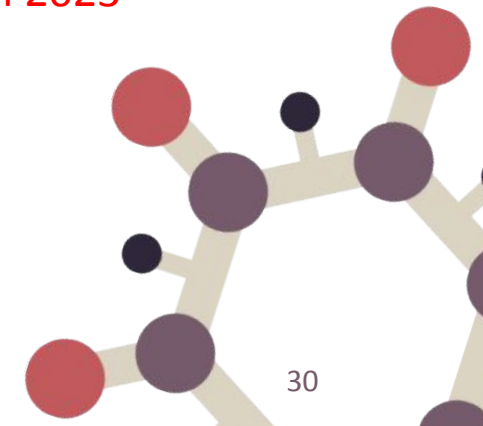
Positive test results in the 2022-2023 surveillance season

Date of sample collection	Location	Virus
12 January 2023	Menindee	Murray Valley encephalitis
12 January 2023	Menindee	Kunjin
19 January 2023	Menindee	Murray Valley encephalitis
20 January 2023	Macquarie Marshes	Murray Valley encephalitis
26 January 2023	Menindee	Murray Valley encephalitis
29 January 2023	Leeton	Murray Valley encephalitis
5 February 2023	Menindee	Murray Valley encephalitis
5 February 2023	Menindee	Kunjin
6 February 2023	Deniliquin	Murray Valley encephalitis
6 February 2023	Forbes	Murray Valley encephalitis
6 February 2023	Hay	Murray Valley encephalitis
6 February 2023	Macquarie Marshes*	Murray Valley encephalitis
12 February 2023	Deniliquin	Murray Valley encephalitis
12 February 2023	Leeton	Murray Valley encephalitis
12 February 2023	Leeton	Kunjin
13 February 2023	Macquarie Marshes	Murray Valley encephalitis
13 February 2023	Macquarie Marshes	Kunjin
14 February 2023	Forbes	Murray Valley encephalitis
19 February 2023	Leeton	Murray Valley encephalitis
19 February 2023	Leeton	Kunjin
21 February 2023	Hay	Murray Valley encephalitis
23 February 2023	West Wyalong	Murray Valley encephalitis
3 March 2023	Deniliquin	Murray Valley encephalitis
5 March 2023	Macquarie Marshes	Kunjin
7 March 2023	Griffith	Murray Valley encephalitis
12 March 2023	Deniliquin	Kunjin
12 March 2023	Menindee	Kunjin
13 March 2023	Leeton	Kunjin
13 March 2023	Moree	Murray Valley encephalitis
13 March 2023	Moree	Kunjin
20 March 2023	Hay	Murray Valley encephalitis
20 March 2023	Hay	Kunjin
26 March 2023	Leeton	Kunjin
2 April 2023	Hay	Kunjin
2 April 2023	Macquarie Marshes	Kunjin
3 April 2023	Griffith	Kunjin
4 April 2023	Forbes	Murray Valley encephalitis
5 April 2023	West Wyalong	Kunjin

*Chickens in Macquarie Marshes had previously seroconverted to Murray Valley encephalitis virus and continue to test positive for antibodies to this virus.

No chickens seroconverting to JEV in 2023

Seroconversions to MVEV & Kunjin demonstrated Jan – April 2023



Mosquito Arbovirus Detections - 2023

Encephalitis virus surveillance trap



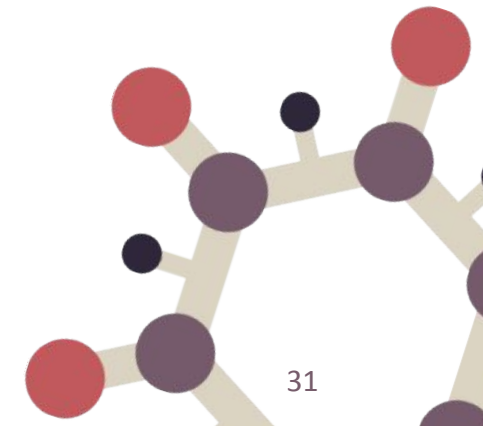
Arboviruses detected in the 2022-2023 surveillance season

Date of sample collection	Location	Virus
14 November 2022	Macquarie Marshes	Barmah Forest
15 November 2022	Griffith	Ross River
22 November 2022	Griffith	Barmah Forest
5 December 2022	Leeton	Barmah Forest
5 December 2022	Temora	Ross River
5 December 2022	Grong Grong	Edge Hill
6 December 2022	Deniliquin	Barmah Forest
6 December 2022	Griffith	Barmah Forest
12 December 2022	Grong Grong	Barmah Forest
13 December 2022	Penrith	Edge Hill
4 January 2023	Menindee	Murray Valley encephalitis
9 January 2023	Corowa	Ross River
9 January 2023	Corowa	Edge Hill
9 January 2023	Young	Barmah Forest
10 January 2023	Griffith	Murray Valley encephalitis
10 January 2023	Menindee	Murray Valley encephalitis
16 January 2023	Griffith	Murray Valley encephalitis
17 January 2023	Mathoura	Murray Valley encephalitis
17 January 2023	Moama	Murray Valley encephalitis
23 January 2023	Macquarie Marshes	Murray Valley encephalitis
23 January 2023	Macquarie Marshes	Kunjin
23 January 2023	Temora	Murray Valley encephalitis
23 January 2023	Griffith	Kunjin
23 January 2023	Balranald	Murray Valley encephalitis
30 January 2023	Albury	Murray Valley encephalitis
30 January 2023	Mathoura	Murray Valley encephalitis
31 January 2023	Leeton	Murray Valley encephalitis
6 February 2023	Griffith	Murray Valley encephalitis
13 February 2023	Macquarie Marshes	Murray Valley encephalitis
13 February 2023	Corowa	Murray Valley encephalitis
19 February 2023	Moree	Edge Hill
20 February 2023	Corowa	Murray Valley encephalitis
21 February 2023	Deniliquin	Murray Valley encephalitis
6 March 2023	Kiama	Stratford
7 March 2023	Wyong	Stratford
7 March 2023	Penrith	Stratford
12 March 2023	Macquarie Marshes	Murray Valley encephalitis
13 March 2023	Narrandera	Ross River
13 March 2023	Georges River	Stratford
21 March 2023	Northern Beaches	Stratford
23 March 2023	Gosford	Barmah Forest
23 March 2023	Gosford	Stratford
3 April 2023	Port Macquarie	Stratford
3 April 2023	Newcastle	Edge Hill
11 April 2023	Newcastle	Edge Hill

Note:
Human cases of Edge Hill virus and Stratford virus have rarely been reported. Infection may present as a mild self-limiting febrile illness with body aches.

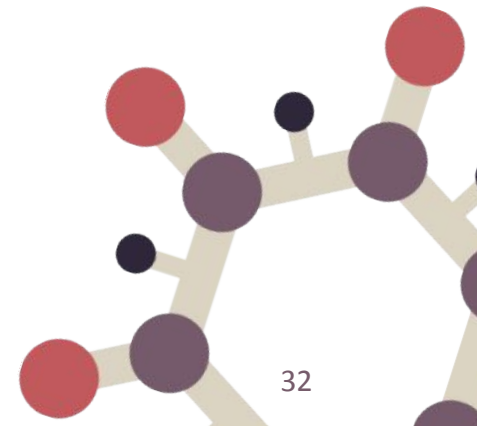
No JEV detections in mosquito grinds in 2023

Numerous MVEV & Kunjin (as well as other viruses) detections from Jan 2023 to present



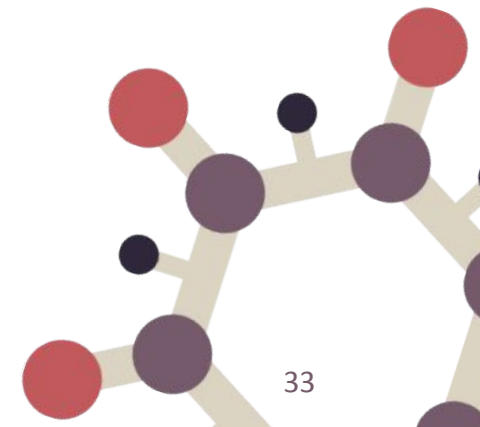
Emergence of Human MVE Cases in 2023

- First two cases diagnosed in January 2023
 - Fatal encephalitis
 - Molecular diagnoses on brain tissue
 - +/- subsequent serological confirmation
- Additional case detections over subsequent months
 - Concentrated in Murray River Region (NSW/VIC) and across WA & NT
 - Fewer cases in SA and QLD
 - Seasonality varies by jurisdiction

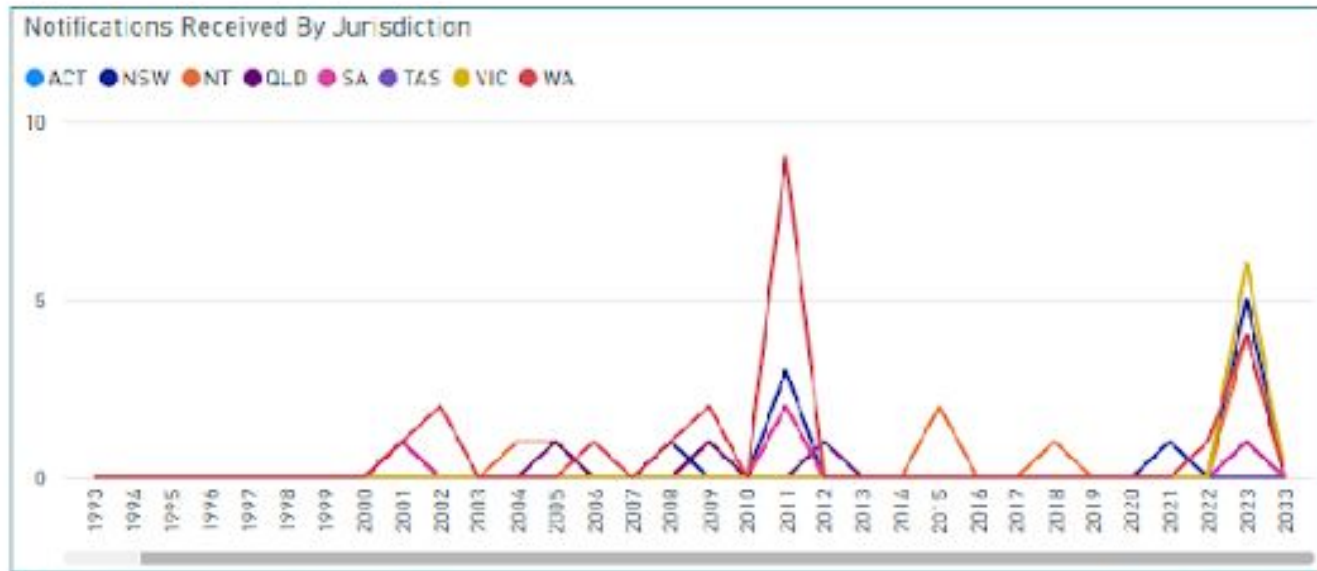


Diagnosis of MVEV

- Majority of cases diagnosed serologically
 - Similar to JEV experience
- Significant “co-positivity” rates with other flaviviruses
 - Overlapping risk factors for prior exposure to Kunjin / JEV
 - Anamnestic responses
 - Known IgM cross-reactivity with other flaviviruses
- Detailed analysis of flavivirus serological profile to achieve diagnosis
 - Specialised expertise required for serological diagnoses



National MVEV Cases: as at 4 June 2023

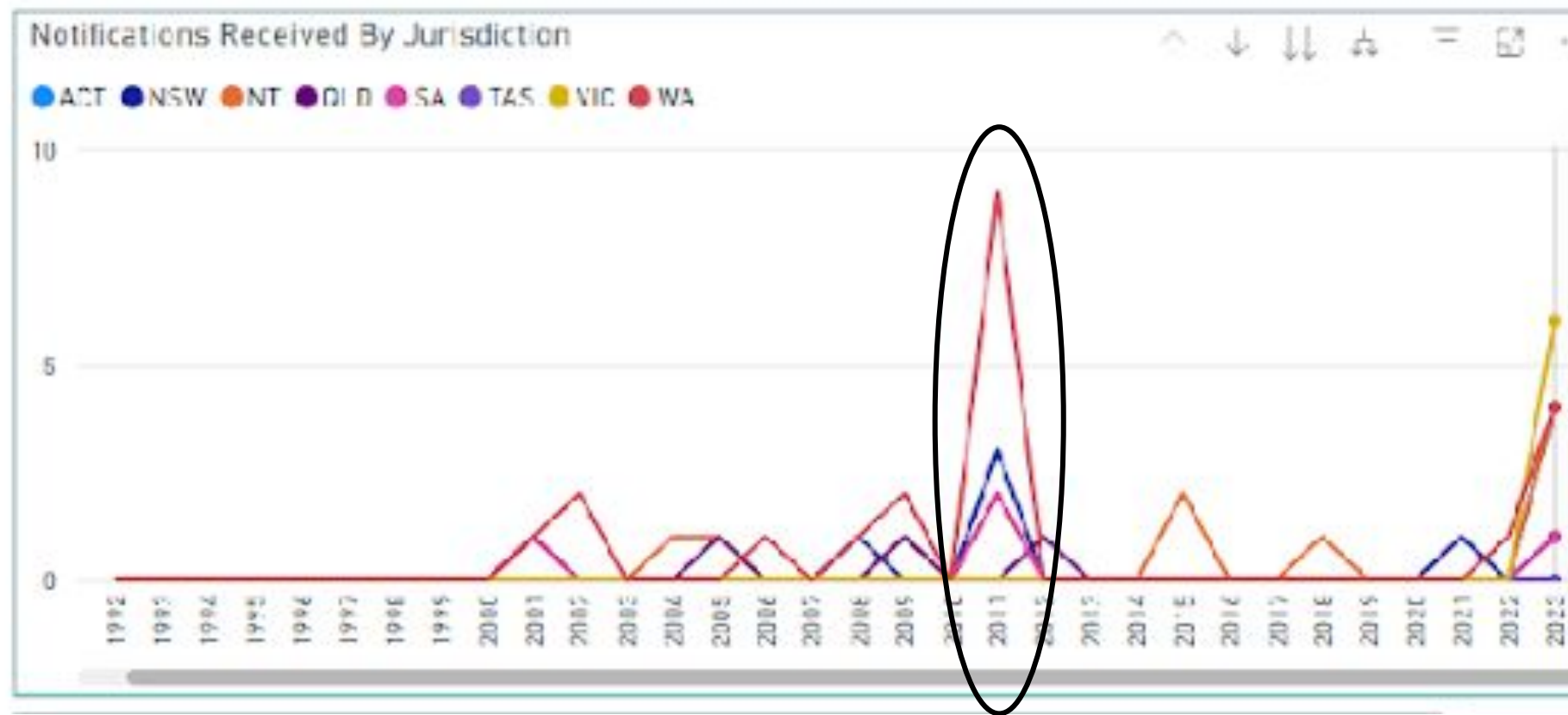


Case Notifications	
NSW	5
VIC	6
SA	1
NT	4
WA	4
QLD	1
TAS	0
Total	21

Case fatality rate: 27-60%
(encephalitic disease)

<https://nindss.health.gov.au/pbi-dashboard/>

MVEV: Lessons from the (recent) past



<https://nindss.health.gov.au/pbi-dashboard/>

MVEV: Lessons from the (recent) past

OPEN ACCESS Freely available online

PLOS NEGLECTED TROPICAL DISEASES

The Changing Epidemiology of Murray Valley Encephalitis in Australia: The 2011 Outbreak and a Review of the Literature

Linda A. Selvey^{1*}, Lynne Dailey², Michael Lindsay³, Paul Armstrong⁴, Sean Tobin⁵, Ann P. Koehler⁶, Peter G. Merkey⁷, David W. Smith⁸

1School of Public Health, Curtin University, Perth, Western Australia, Australia, **2**Independent consultant, Perth, Western Australia, Australia, **3**Environmental Health Directorate, WA Health, Perth, Western Australia, Australia, **4**Communicable Disease Control Directorate, WA Health, Perth, Western Australia, Australia, **5**Communicable Diseases Branch, Health Protection NSW, NSW Health, Sydney, New South Wales, Australia, **6**Communicable Disease Control Branch, SA Department for Health and Aging, Adelaide, South Australia, Australia, **7**Centre for Disease Control, Department of Health, Northern Territory, Australia, **8**School of Pathology and Laboratory Medicine, Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia, Perth, Western Australia, Australia

Abstract

Murray Valley encephalitis virus (MVEV) is the most serious of the endemic arboviruses in Australia. It was responsible for six known large outbreaks of encephalitis in south-eastern Australia in the 1900s, with the last comprising 58 cases in 1974. Since then MVEV clinical cases have been largely confined to the western and central parts of northern Australia. In 2011, high level MVEV activity occurred in south-eastern Australia for the first time since 1974, accompanied by unusually heavy seasonal MVEV activity in northern Australia. This resulted in 17 confirmed cases of MVEV disease across Australia. Record wet season rainfall was recorded in many areas of Australia in the summer and autumn of 2011. This was associated with significant flooding and increased numbers of the mosquito vector and subsequent MVEV activity. This paper documents the outbreak and adds to our knowledge about disease outcomes, epidemiology of disease and the link between the MVEV activity and environmental factors. Clinical and demographic information from the 17 reported cases was obtained. Cases or family members were interviewed about their activities and location during the incubation period. In contrast to outbreaks prior to 2000, the majority of cases were non-Aboriginal adults, and almost half (40%) of the cases acquired MVEV outside their area of residence. All but two cases occurred in areas of known MVEV activity. This outbreak continues to reflect a change in the demographic pattern of human cases of encephalitic MVEV over the last 20 years. In northern Australia, this is associated with the increasing numbers of non-Aboriginal workers and tourists living and travelling in endemic and epidemic areas, and also identifies an association with activities that lead to high mosquito exposure. This outbreak demonstrates that there is an ongoing risk of MVEV encephalitis to the heavily populated areas of south-eastern Australia.

Citation: Selvey LA, Dailey L, Lindsay M, Armstrong P, Tobin S, et al. (2014) The Changing Epidemiology of Murray Valley Encephalitis in Australia: The 2011 Outbreak and a Review of the Literature. PLoS Negl Trop Dis 8(1): e2656. doi:10.1371/journal.pntd.0002656

Editor: Matthew Kasper, U.S. Naval Medical Research Unit Six, United States of America

Received: August 15, 2013; **Accepted:** December 4, 2013; **Published:** January 23, 2014

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Funding: The authors received no specific funding for this study.

Competing interests: The authors have declared that no competing interests exist.

* Email: lindaselvey@curtin.edu.au

Murray Valley Encephalitis in Australia 2011

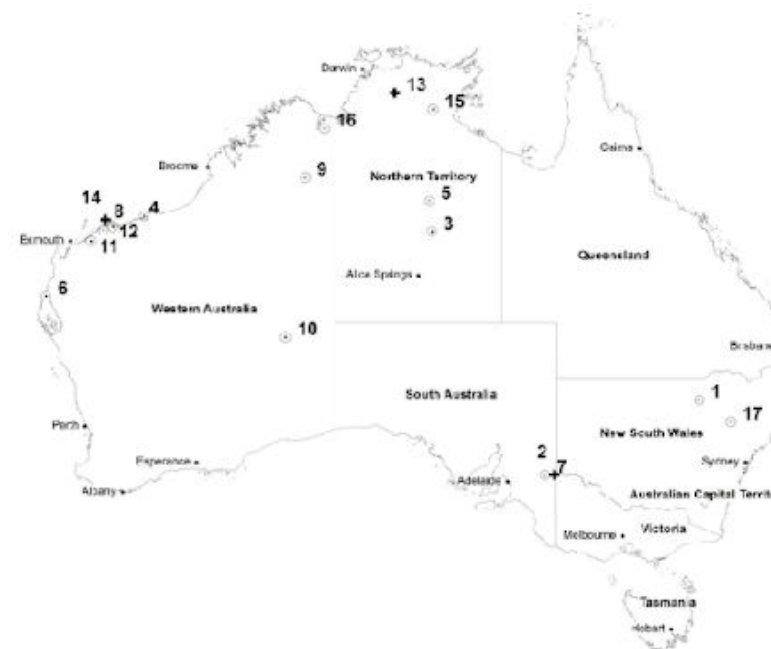


Figure 1. Geographical distribution of MVEV cases in Australia 2011. Legend: Each circle with a dot inside represents a case who survived; Each black cross represents a case who died. Note: cases 11 and 12; 2 and 7; and 8 and 14 occurred in the same location, and the symbols are shown side by side.
doi:10.1371/journal.pntd.0002656.g001

Vaccination for MVEV & other encephalitic flaviviruses

No available vaccine for MVEV

Increased interest in development of vaccines to range of flaviviruses

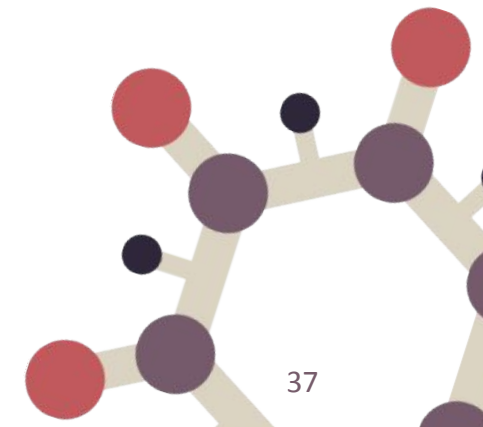


Perspective
MAY 4, 2023

Combating West Nile Virus Disease — Time to Revisit Vaccination

Carolyn V. Gould, M.D., J. Erin Staples, M.D., Claire Y.-H. Huang, Ph.D., Aaron C. Braub, Ph.D., and Randall J. Neth, M.D.

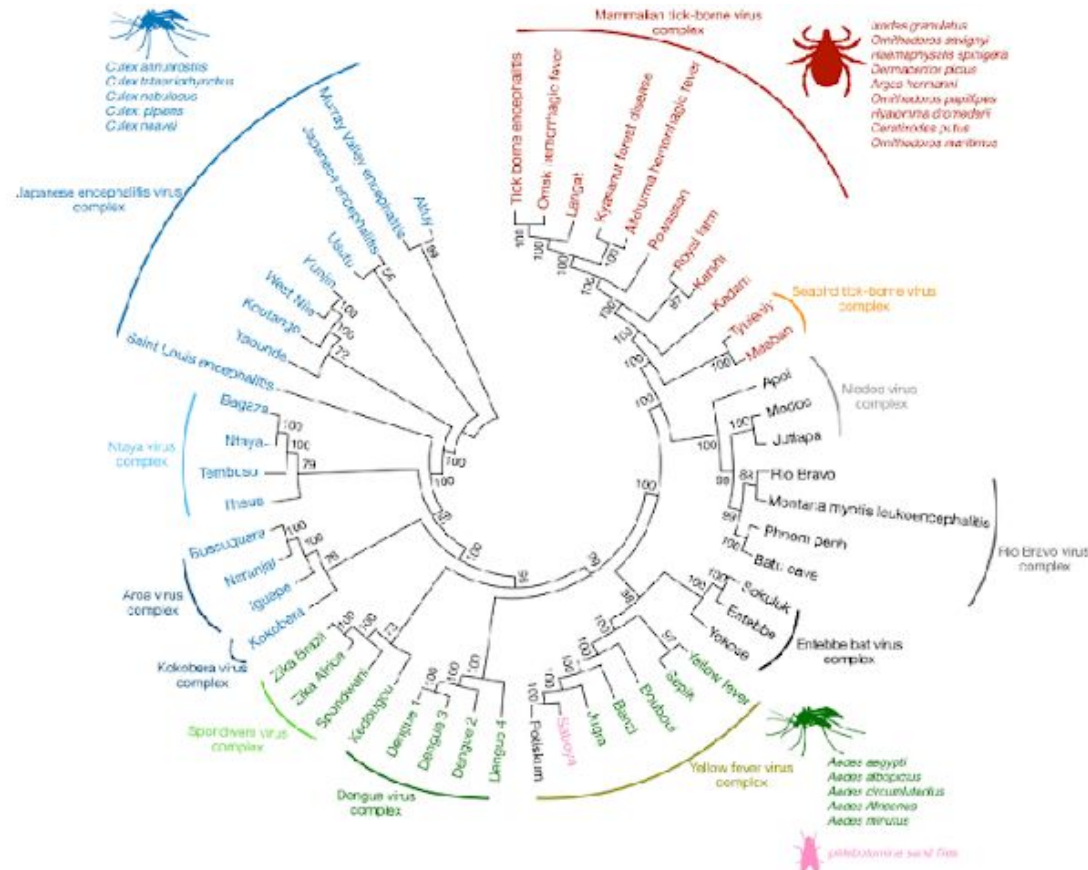
immunisationcoalition.org.au



Flavivirus Vaccination Cross-Protection

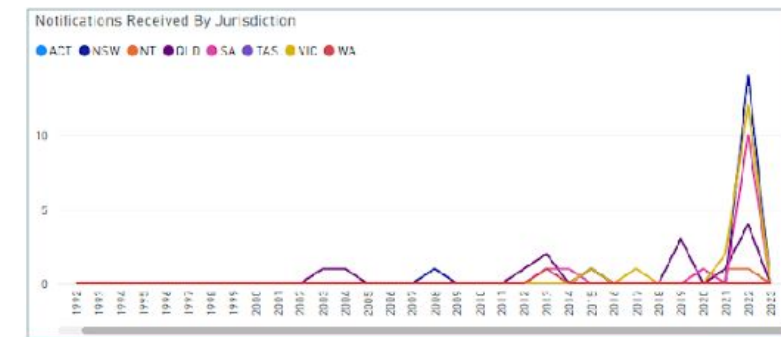
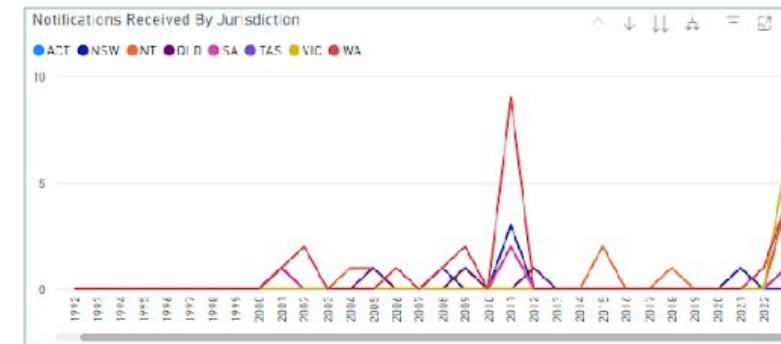
Flavivirus-specific immunity is complex

Animal studies suggest cross-reactive immunity within the JEV serocomplex (JEV/MVEV/WNV/St Louis)



Flavivirus Circulation in Australia: 2023

- Increase in case detections of **MVEV** in 2023
 - High correlation with chicken seroconversions and mosquito detections
 - Clinically: encephalitic disease carries high mortality & morbidity
- No human cases of **JEV** diagnosed in 2023 season
- No encephalitic cases of **Kunjin** diagnosed
 - Consistent with expected spectrum of disease



Conclusions

Diagnosis of JEV, MVEV and Kunjin is complex

Serological (acute + convalescent) and molecular testing are highly complementary tools for flavivirus diagnosis

Accurate diagnosis requires integration of:

- Clinical presentation
- Local epidemiology
- Patient's travel / exposure / vaccination history -> bespoke flavi "panel"
- Understanding of assay parameters
- Inter-laboratory collaboration

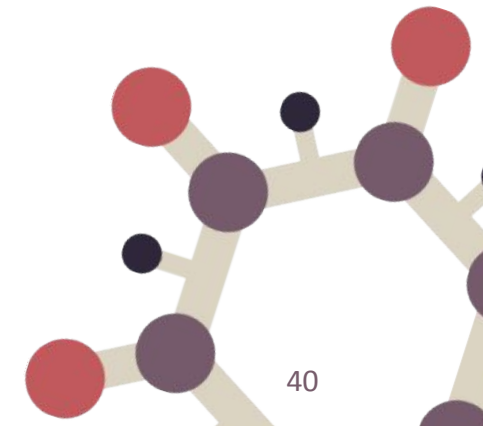
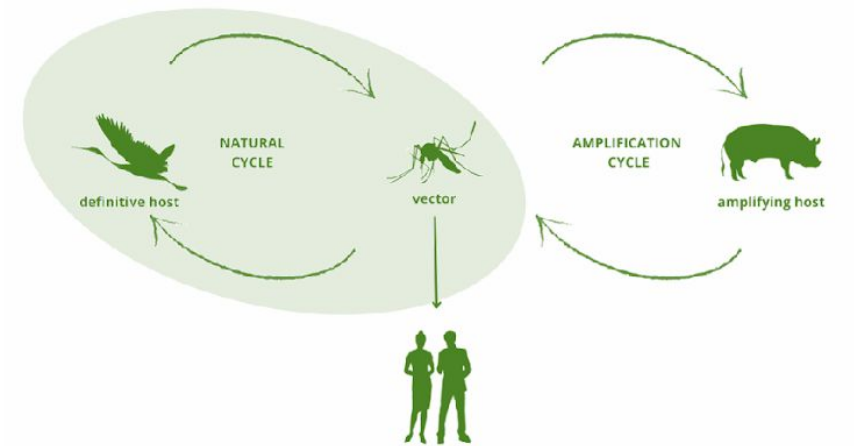
Australian flavivirus landscape is in evolution and subject to environmental influences

- Questions of endemicity remain open (JEV)

Vaccination and education of at-risk populations is critical

Potential OneHealth lessons / opportunities abound

- Interplay of vector-animal-human transmission dynamics + climate factors
- Drivers of apparent in-vector arbovirus predominance



Acknowledgements

NSW Health Pathology-ICPMR

Dominic Dwyer *

Jen Kok

Susan Maddocks

Matthew O'Sullivan

David Pham

Neisha Jeoffreys

Linda Hueston

Cameron Webb *

Stephen Doggett

WIMR

John-Sebastian Eden

Referring clinicians & laboratories across NSW

Collaborating laboratories in other states

