



# The Dubbo Infection Outcomes Study

Determinants of protracted illness  
after acute infection

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## Three parallel cohorts

### ● Epstein-Barr virus:

- infectious mononucleosis
- established model of post-infection fatigue (PIFS)
- natural persistence of the organism via latency

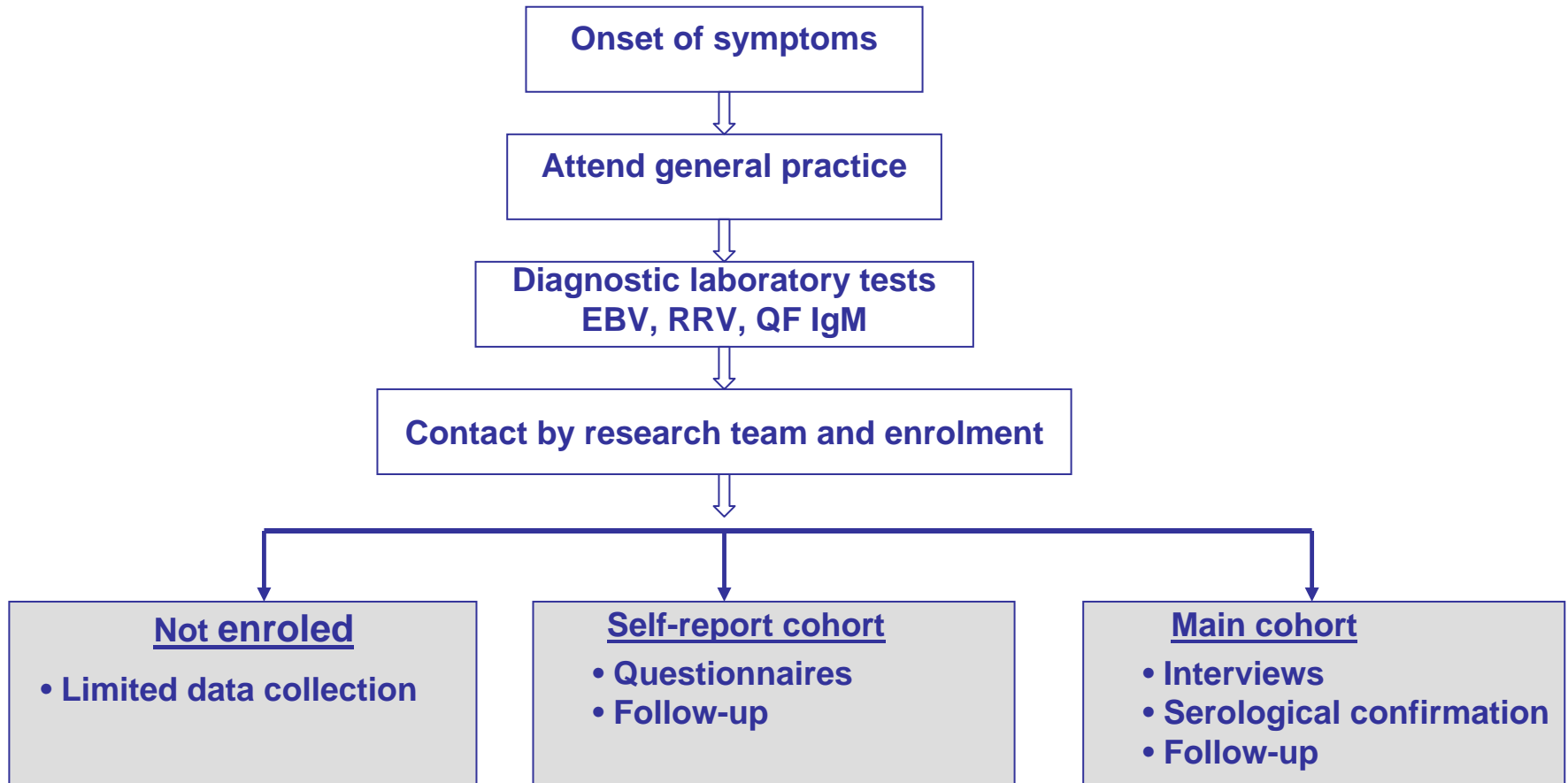
### ● Ross River virus:

- mosquito-borne seasonal infection
- rash and arthritis
- linked to a prolonged musculo-skeletal pain syndrome

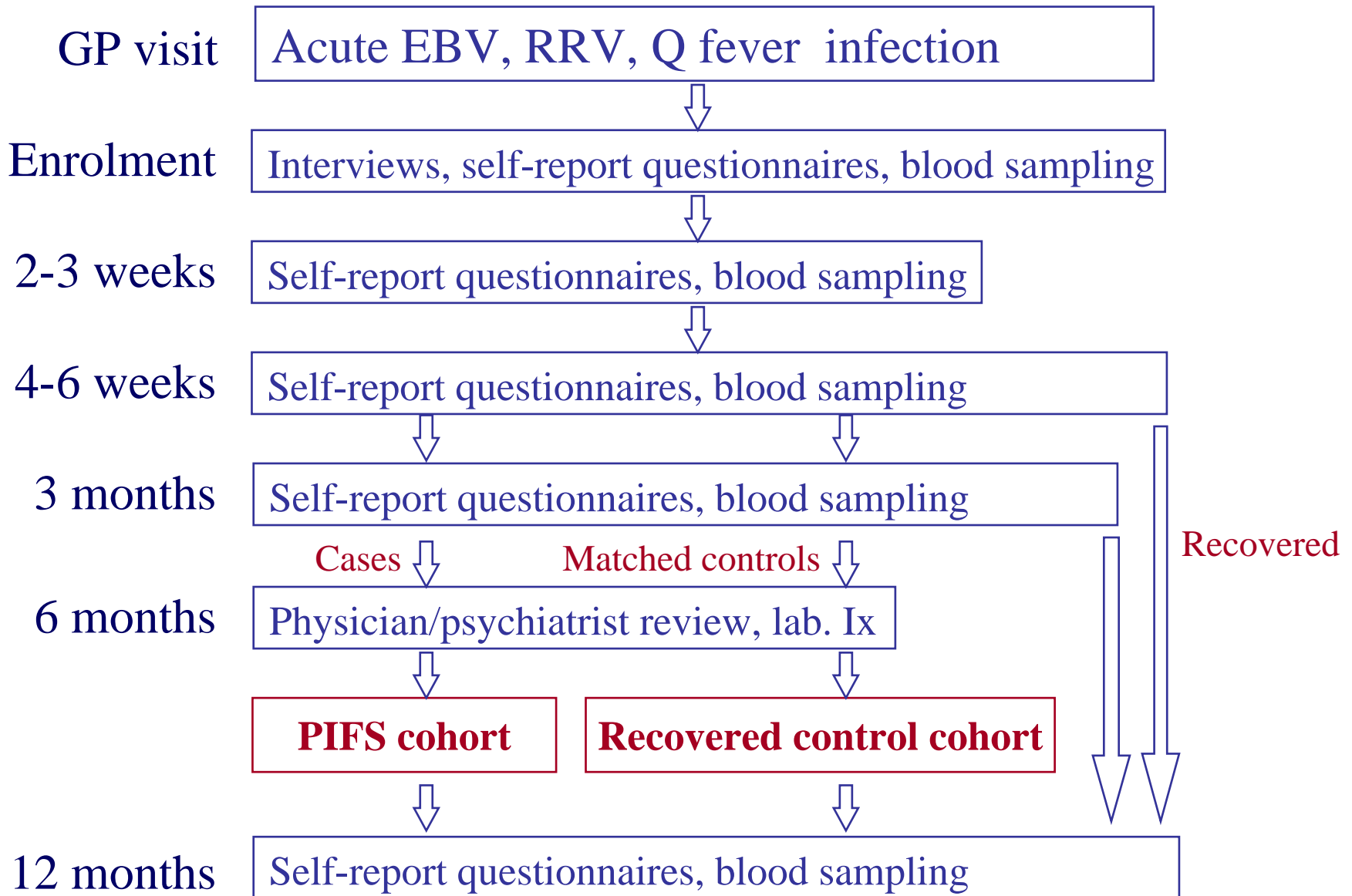
### ● Q fever:

- zoonotic infection caused by *Coxiella burnetii*
- severe acute illness with hepatitis and pneumonia
- rare long-lasting chronic, localised infections

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# Dubbo Infection Outcomes Study - main cohort



# Characteristics of the cohort (n=254)

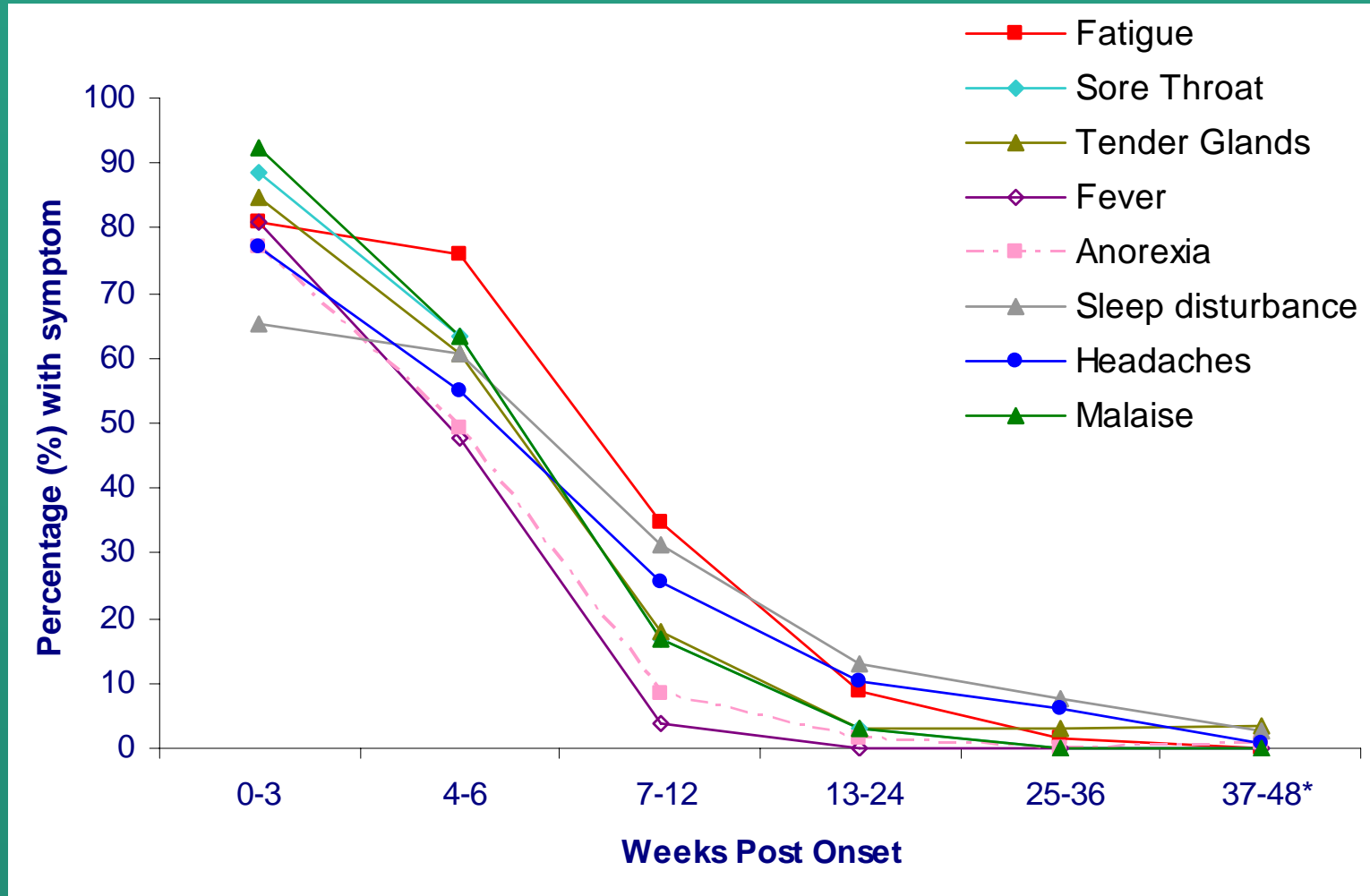
	<u>EBV</u>	<u>RRV</u>	<u>QF</u>	<u>Unconf.</u>
Sample size (n)	68	60	45	81
Age (mean; yrs)	22	40	40	38
Sex (% female)	57	45	13	44
Education (%<10 yrs)	23	43	52	43
Employed (%)	45	81	95	76
Student (%)	49	2	3	10

# Natural history of symptoms in acute EBV



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Confirmed EBV (n=68)

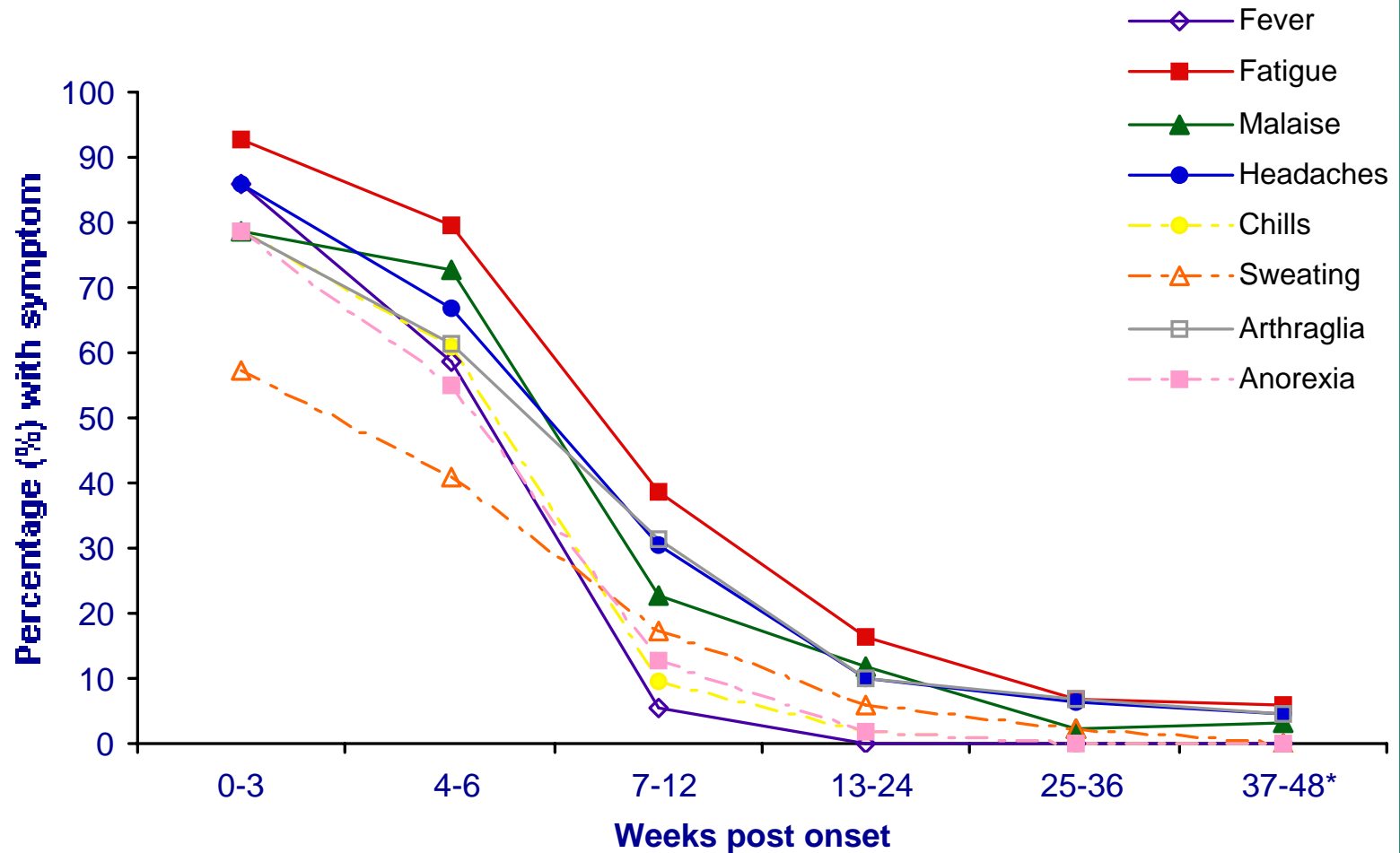


# Natural history of symptoms in acute QF



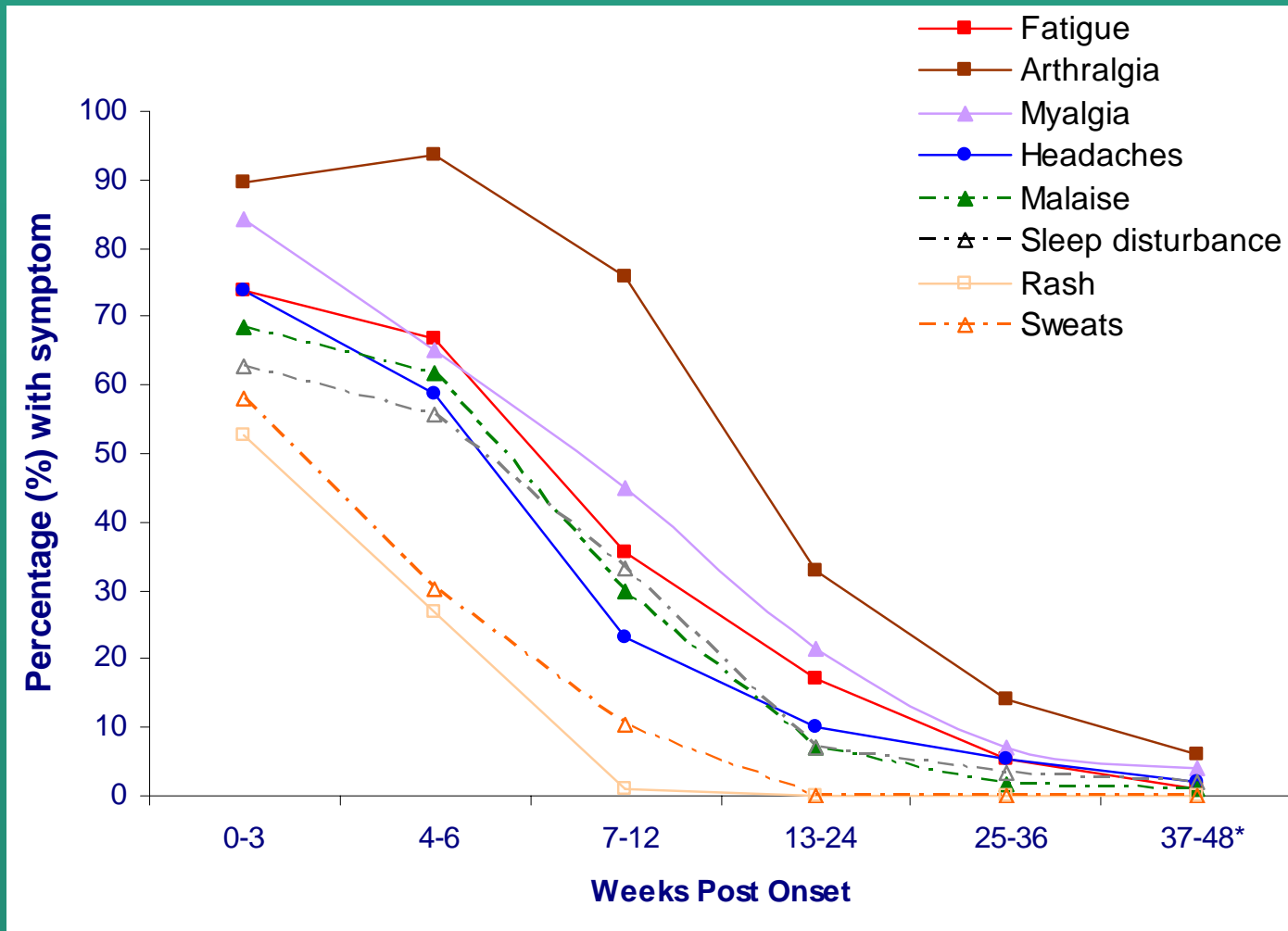
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Confirmed QF (n=45)



# Natural history of symptoms in acute RRV

Confirmed RRV (n=60)





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## Conclusions - outcomes data

- Prolonged illness is common after EBV, RRV, Q fever
- Fatigue, musculo-skeletal pain are features

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## Hypothesis testing

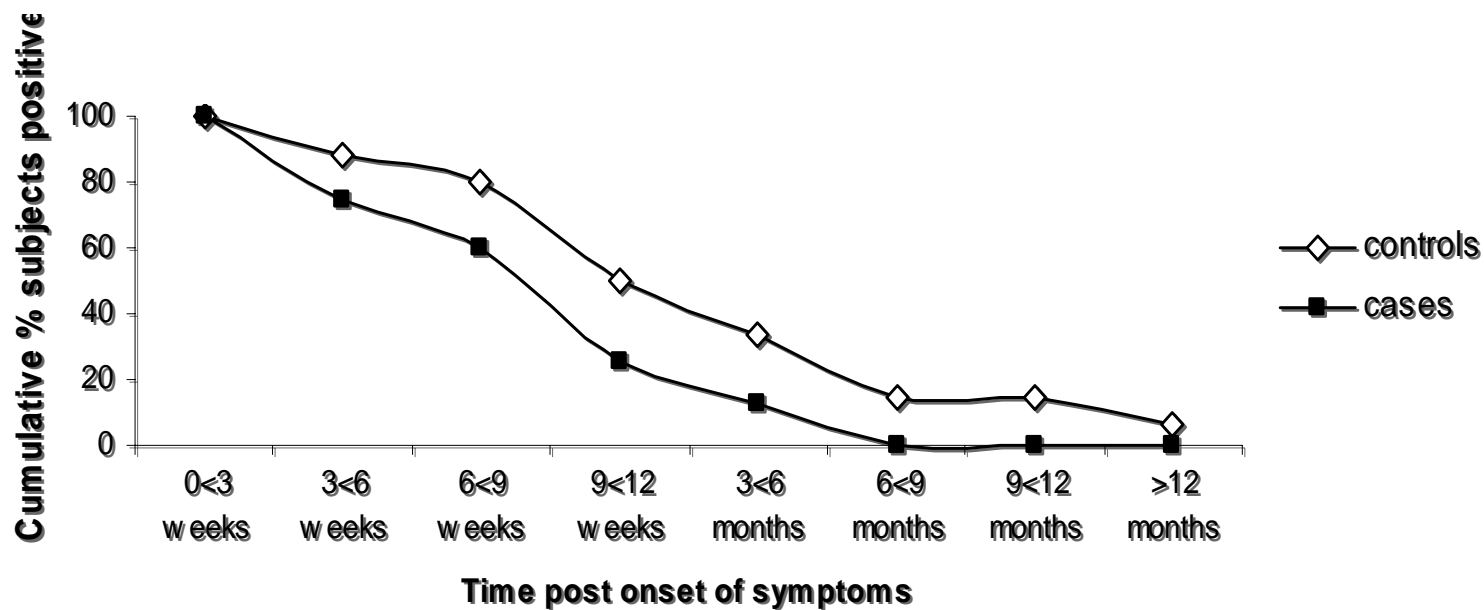
- Case-control series
  - cases: six months of more of disabling illness
  - controls: matched by age, sex, pathogen; prompt recovery
- Longitudinally collected samples and data:
  - psychological factors
  - microbiological factors
  - immunological factors
  - genetic factors

# EBV case-control series



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## Persistence of anti-VCA IgM

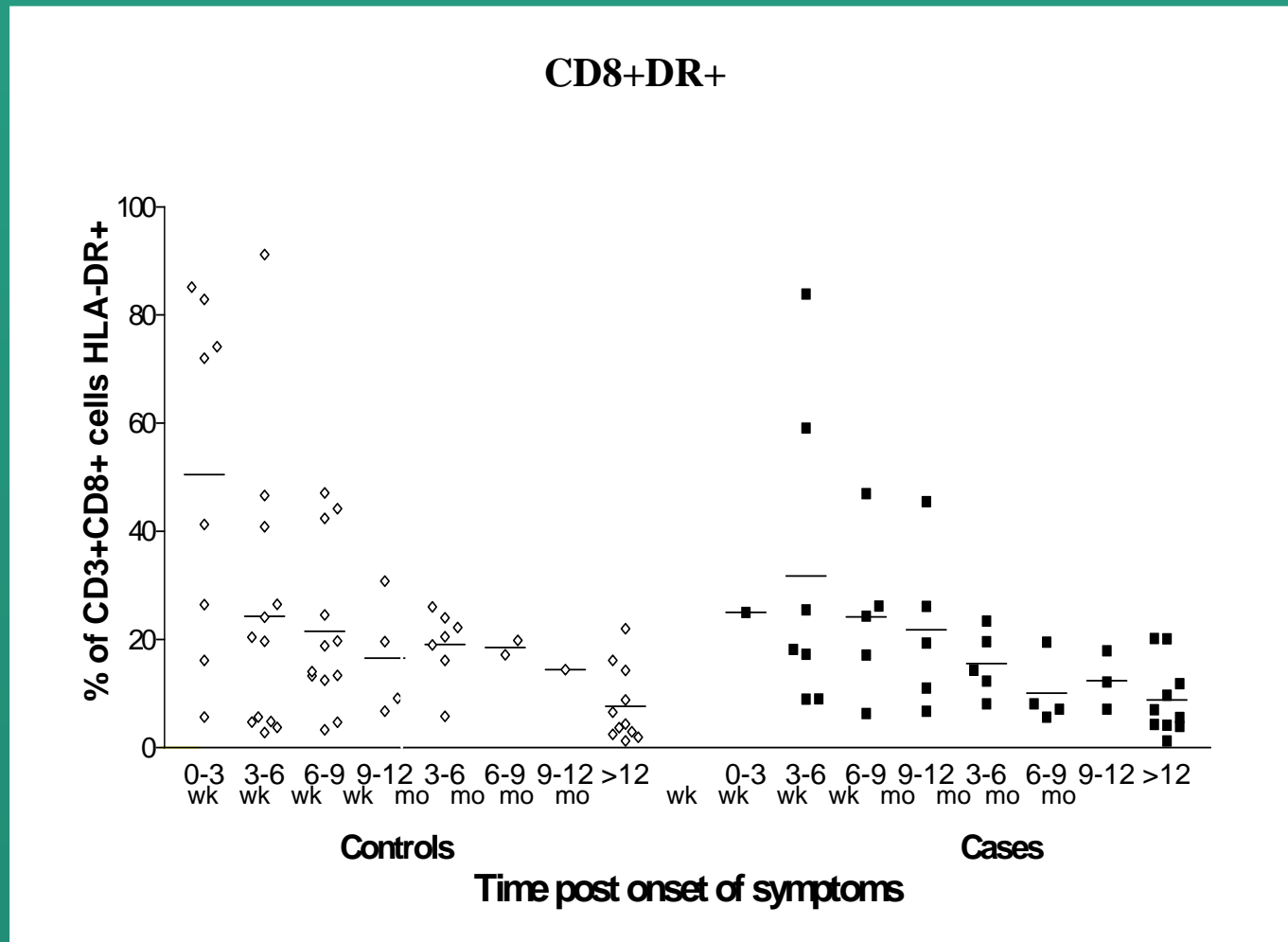


# EBV case-control series



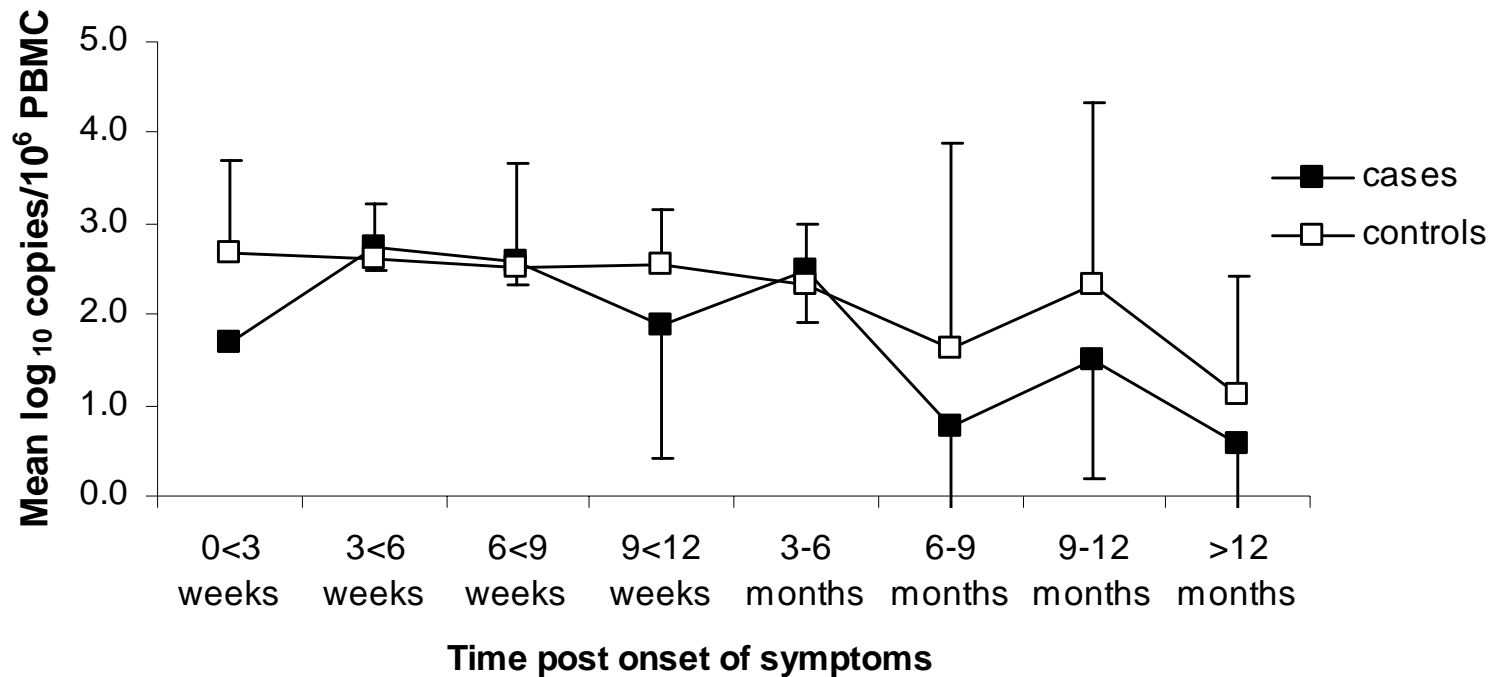
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## Leucocyte subsets and their activation



# EBV case-control series

## EBV cellular viral load



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## Pathogenesis: case-control series

- No evidence for abnormal persistence of organism
- No significant difference in the immune response
- Psychological disorder not a risk factor

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## Avidity studies

- Serological diagnosis of primary infection based on a single IgM antibody result is unreliable
- IgG avidity for antigen matures in primary immune responses
- Relevance to EBV and RRV diagnoses

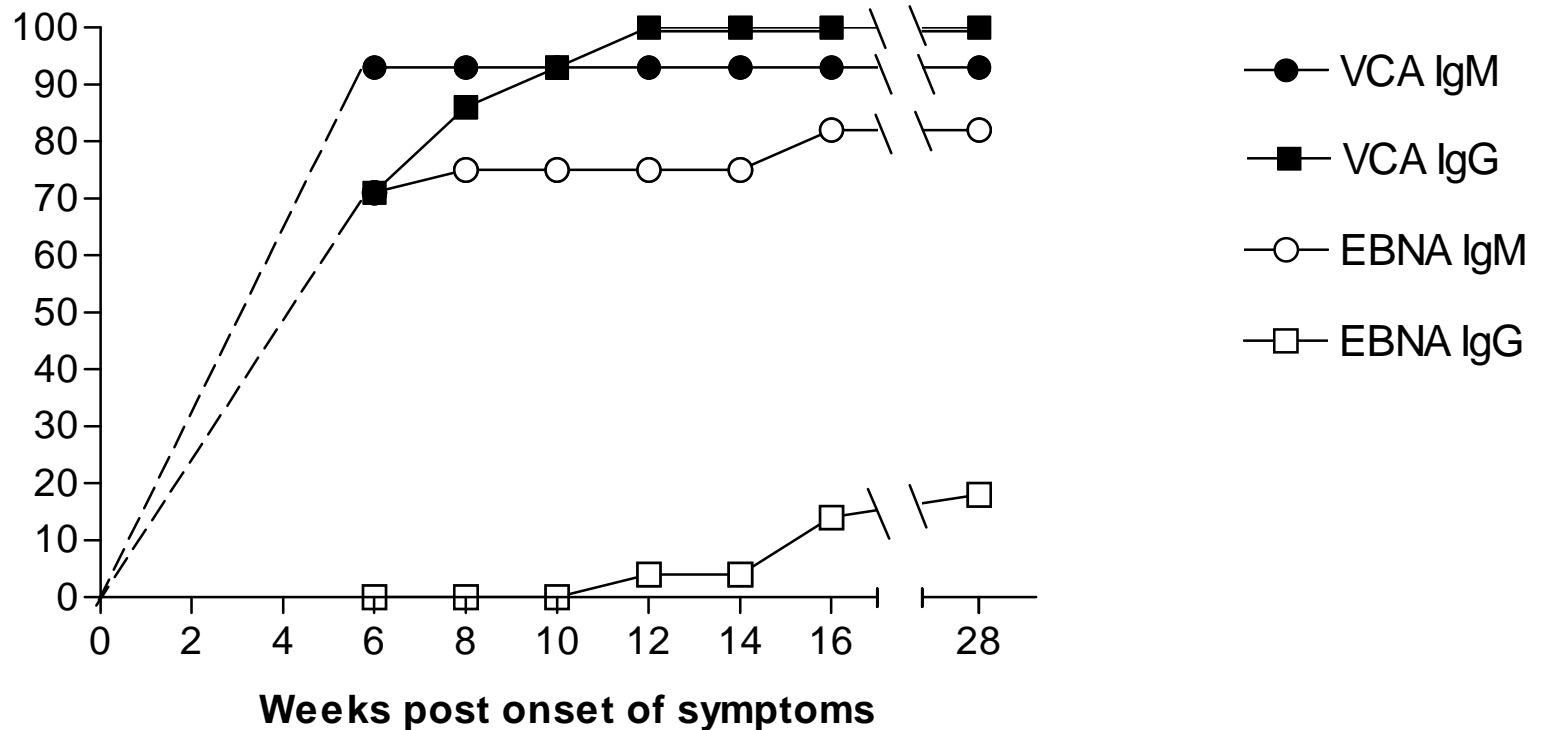
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## Serological responses

### EBV





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## Avidity studies - EBV

- 28 subjects with clinical diagnosis of glandular fever and consistently positive IgM anti-VCA or IgG seroconversion
- 35 subjects with pre-existing IgG anti-VCA and confirmed hepatitis A, HIV or CMV infection
- EBV IgG anti-VCA, IgM anti-VCA
- EBV IgG anti-VCA avidity (8M urea)

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## Serological responses (IgG VCA avidity)

Number (%) of group with positive  
serology

	Sample size (n)	VCA		EBNA		Mean IgG VCA avidity (SD)
		IgG	IgM	IgG	IgM	
Hepatitis A	15	15 (100)	12 (80)	15 (100)	12 (80)	95 (5.7)
HIV	14	14 (100)	5 (36)	14 (100)	10 (71)	98 (2.8)
CMV	6	6 (100)	1 (16)	6 (100)	6 (100)	96 (3.2)
Combined	35	35 (100)	18 (51)	35 (100)	28 (80)	96.3 (4.4)

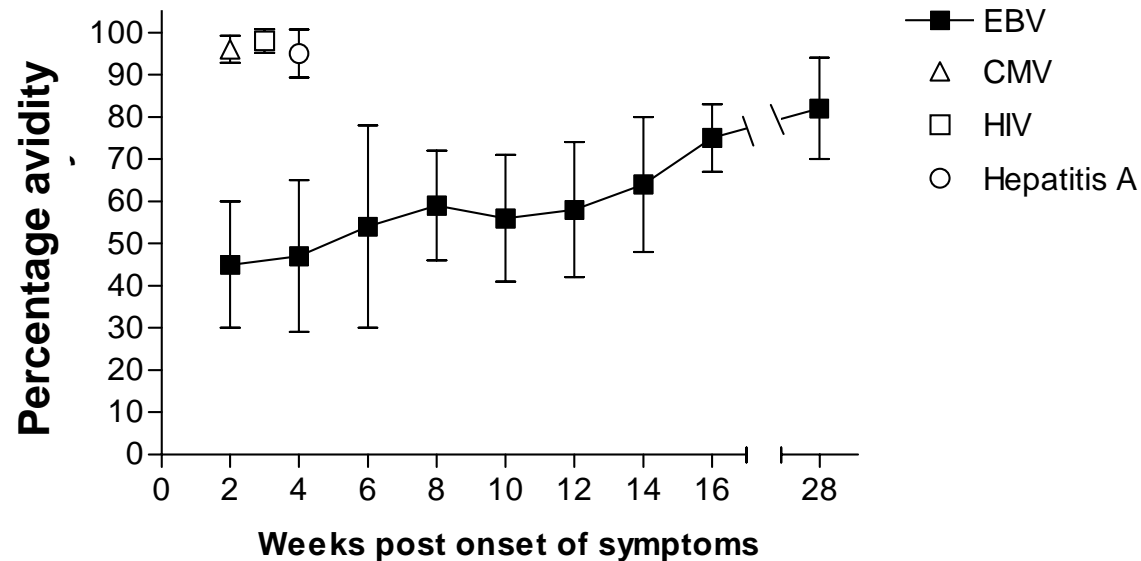
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## Serological responses (IgG VCA avidity)

### EBV



Number of samples

from EBV cases tested: n = 7 15 22 17 13 5 2 5 4

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## Avidity studies - EBV

- IgM anti-VCA:
  - sensitivity 100%
  - specificity 49% (14 of 35 false positives)
- IgM anti-VCA + low avidity IgG anti-VCA:
  - sensitivity 93%
  - specificity 97%

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## Avidity studies - RRV

- 89 subjects with clinical RRV infection and RRV IgM
- 88 subjects with confirmed EBV or QF infection and IgG anti-RRV

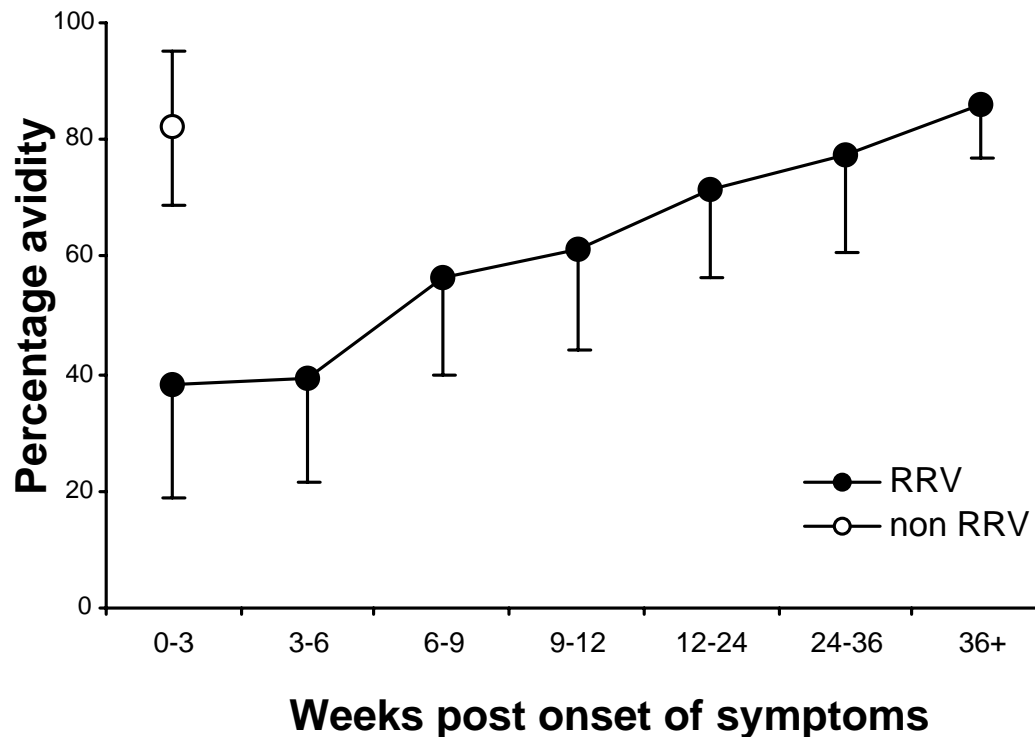
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## Serological responses (IgG RRV avidity)

### RRV



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## Avidity studies - RRV

- IgM anti-RRV:
  - sensitivity 100%
  - specificity 78% (19 of 88 sera false positive)
- IgM anti-RRV + low avidity IgG anti-RRV:
  - sensitivity 92%
  - specificity 100%

# Research team

## Dubbo Study

- Maree Wilkinson, Sue Newham, Valma Cahill (Dubbo - field & laboratory)
- Justine Diver (UNSW - admin)
- Ian Hickie, Tracey Davenport (USyd - Psych)
- Barb Cameron (UNSW - Immunology)
- Ute Vollmer-Conna (UNSW - Psycho-immunology)

## Collaborators:

- Rajiv Khanna, Mandvi Bharadwaj (QIMR - EBV)
- Barrie Marmion, Ray Harris (IMVS - QF)
- Heather Dunckley, Andrew Geczy (ARCBS - Genetics)
- Bill Reeves, Suzanne Vernon, Toni Whistler, (CDC - Gene expression)
- Peter Robertson, Ross Whybin, Bill Rawlinson (SEALS - avidity studies)