STREPTOCOCCAL SEROLOGY IN ACUTE RHEUMATIC FEVER PATIENTS:
FINDINGS FROM TWO HIGH-INCOME, HIGH BURDEN SETTINGS

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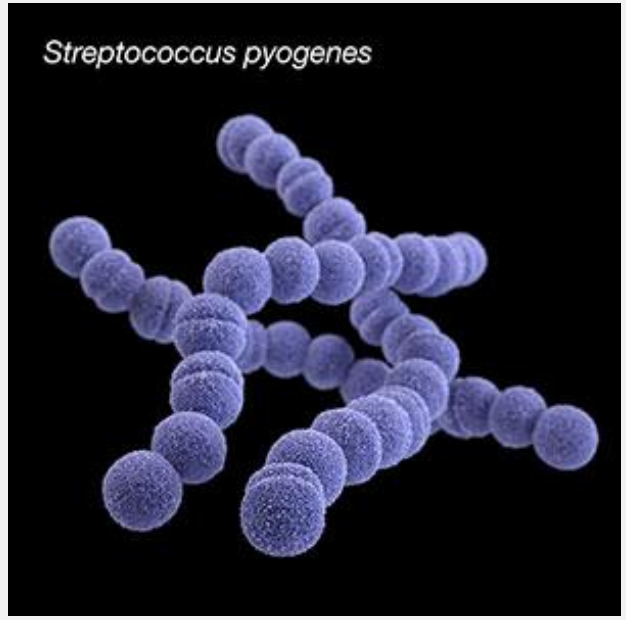
BACKGROUND

- Absence of a definitive diagnostic test for acute rheumatic fever
- Diagnosis relies on meeting Jones criteria (clinical guide) plus evidence of preceding Strep A infection
  - Two-fold rise in streptococcal titres between acute and convalescent sera
  - Upper limit of normal (ULN) titre cut-offs used where sequential sera samples are not possible
  - ULN cut-offs 80th percentile of titre values in a healthy population

CHALLENGES IN ESTABLISHING ULN



https://www.cdc.gov/streplab/groupa-strep/index.html

- Differing characteristics of available assays – no globally accepted standard
- Antistreptolysin O (ASO) and antideoxyribonuclease B (ADB) can remain elevated for many weeks following an infection
- Sub-clinical infection means a proportion of 'healthy' populations may have elevated values
- Non-group A beta-haemolytic strep can also cause elevated ASO titres

UPPER LIMITS OF NORMAL STREP TITRES IN NZ

- ULN cut-offs for NZ generated from a paediatric (<15 years) hospital population admitted for reasons other than ARF/RHD in Auckland in 1982
- Single all-age ULN for ASO and ADB
- NZ ULN cut-off higher than recommended elsewhere globally
- Concern that if strep titre cut-offs are too high, genuine cases of ARF may be missed

COMPARISON OF STREP TITRE ULN CUT-OFFS

Data or guideline place and date	Age group (years)	ASO titre (IU/ml)	ADB titre (U/ml)
New Zealand study 1982 and guideline 2014	All ages	≥480	≥680
Australia (urban, non-indigenous), 2005 and Australian guideline 2006	4–5 6–9 10–14	120 480 320	100 400 380
Fijian study 2009 and Australian guideline 2012	1–4 5–14 15–24 25–34 >35	170 276 238 177 127	366 499 473 390 265

AIMS

- Determine the proportion of cases fulfilling diagnostic guidelines in NZ and Australia's Northern Territory (NT) respectively
- Determine whether the currently-recommended local guidelines for ASO and ADB are being applied
- Calculate the proportion of cases fulfilling alternative serologic diagnostic criteria.

METHODS

NEW ZEALAND

- Retrospective audit of serologic results from notified ARF cases Jan 2013–December 2015
- Highest recorded titre level was used
- Applied NZ clinical case definitions with NZ ULN cut-offs compared with Australian cut-offs

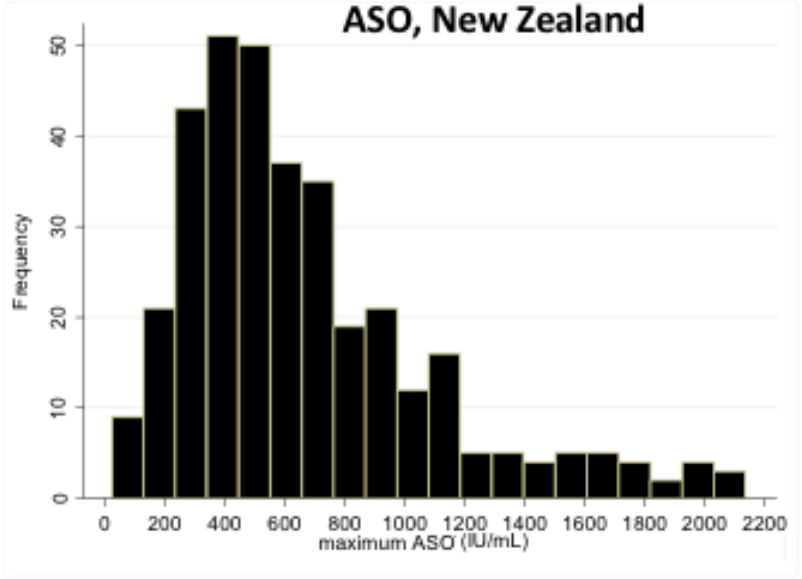
NOTHERN TERRITORIES

- Retrospective audit of serologic results from ARF cases on the NT register Jan 2013–December 2015
- Recorded titre levels were used with dates
- Applied Australian clinical case definitions with Australian ULN cut-offs compared with NZ cut-offs

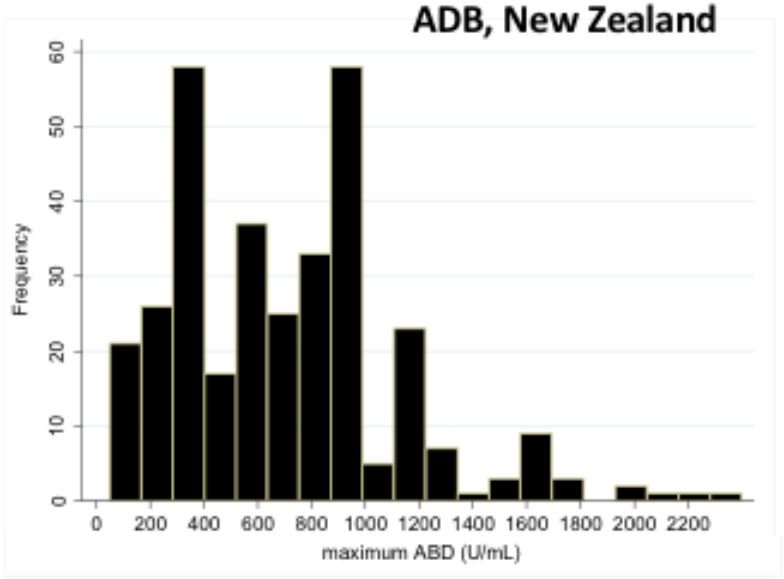
CLINICAL CHARACTERISTICS OF ARF CASES

		New Zealand: n (%)		Northern Territory, Australia: n (%)	
Age in years: geometric mean (95% CI)		12.3 (11.7 to 12.9)		12.3 (11.4-13.3)	
Female		166	(47.4)	103	(52.6)
Diagnosis	Definite ARF	262	(74.9)	152	(77.6)
	Probable ARF	37	(10.6)	23	(11.7)
	Possible ARF	51	(14.6)	21	(10.7)
ARF type	First episode	323	(92.3)	139	(70.9)
	Recurrence	27	(7.7)	57	(29.1)
Total		**350**	**(100)**	**196**	**(100)**
Median peak ASO titre	IU/ml (IQR)	562	(337–754)	610	(400–913)
Median peak ADB titre	IU/ml (IQR)	599	(300–900)	600	(400–850)

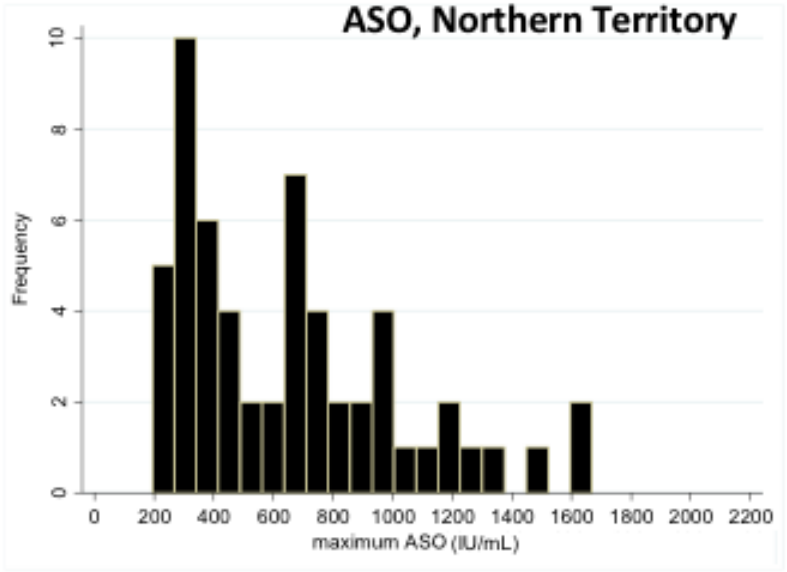
A


ASO, New Zealand
Frequency
0
10
20
30
40
50
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200
maximum ASO (IU/mL)

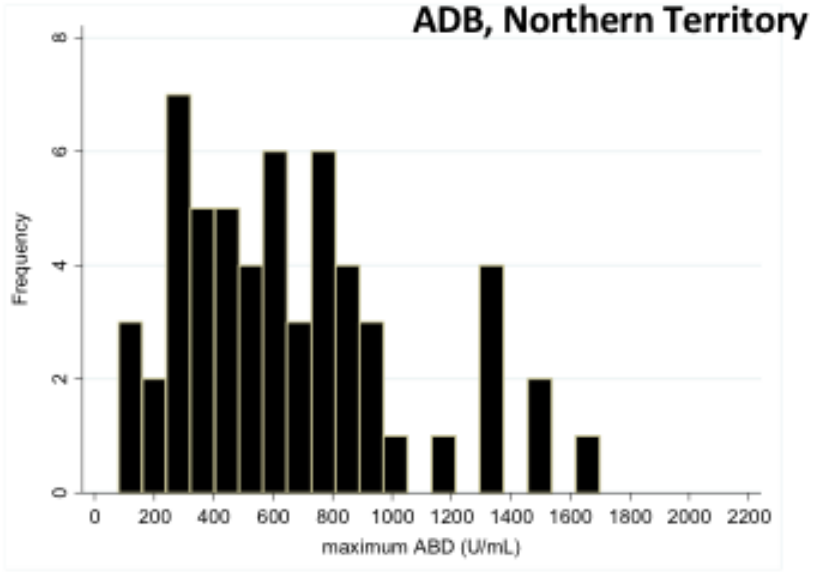
B


ADB, New Zealand
Frequency
0
10
20
30
40
50
60
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200
maximum ABD (U/mL)

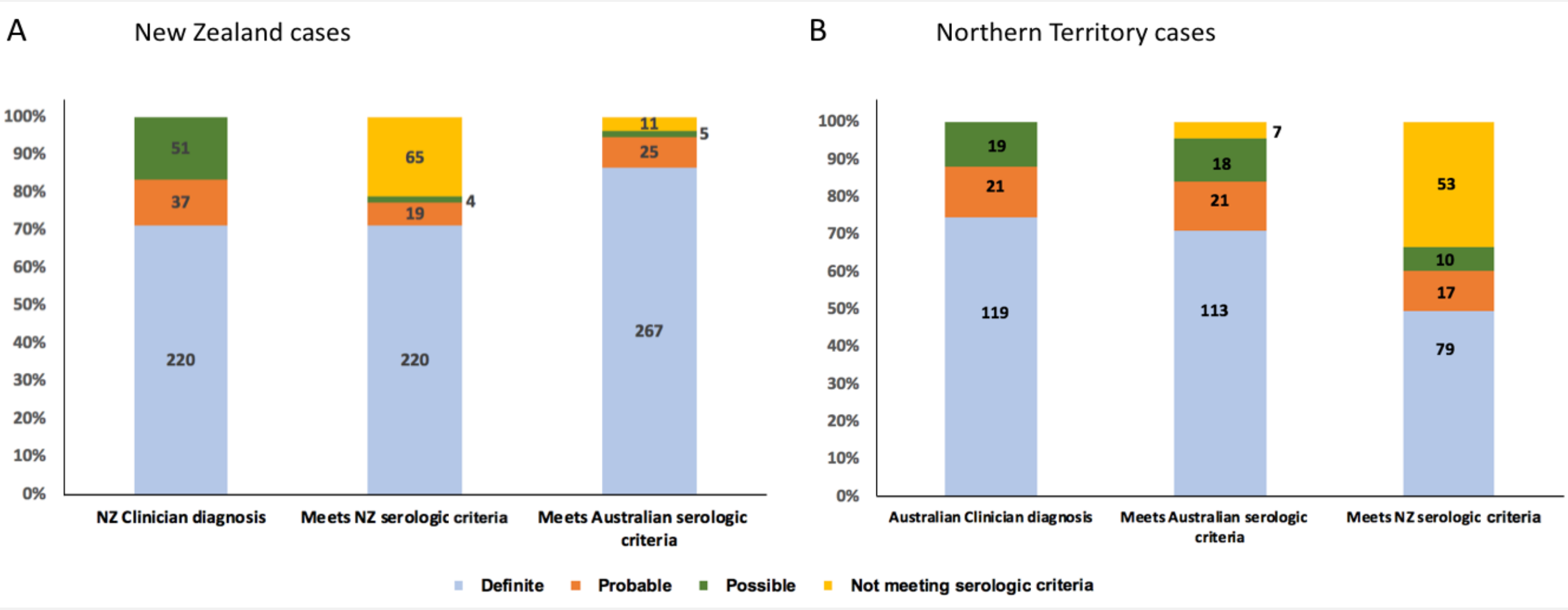
C


ASO, Northern Territory
Frequency
0
2
4
6
8
10
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200
maximum ASO (IU/mL)

D


ADB, Northern Territory
Frequency
0
2
4
6
8
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200
maximum ABD (U/mL)

ARF CASES WITH DIFFERENT DIAGNOSTIC CRITERIA APPLIED (EXCLUDING CHOREA CASES)



CONCLUSIONS

- Similar clinical and ASO and ADB profiles are observed among high risk populations in NZ and Australia
- Strict application of NZ serologic criteria would result in under-counting ARF cases
- NZ clinicians diagnosing ARF appropriately despite strep titres not meeting high NZ ULN cut-offs
- Unable to determine if some ARF cases are missed as only audited notified or registered cases were included
- If we applied Australian ULN strep titre cut-offs to NZ ARF cases (excluding chorea), ARF definite cases would increase by 18% representing 47 cases over three years

NZ should consider either:

- Updating their guidelines using age-specific titre ULN used in Australia, or
- Conducting a study to ascertain contemporary NZ age-specific strep titre ULN cut-offs