

# **Vitamin D deficiency and Latent Tuberculosis in refugee children:**

## **A POSITIVE ASSOCIATION**

Stewart Birt  
Nick Wood  
Mohamud Sheikh  
Hasantha Gunasekera  
David Isaacs

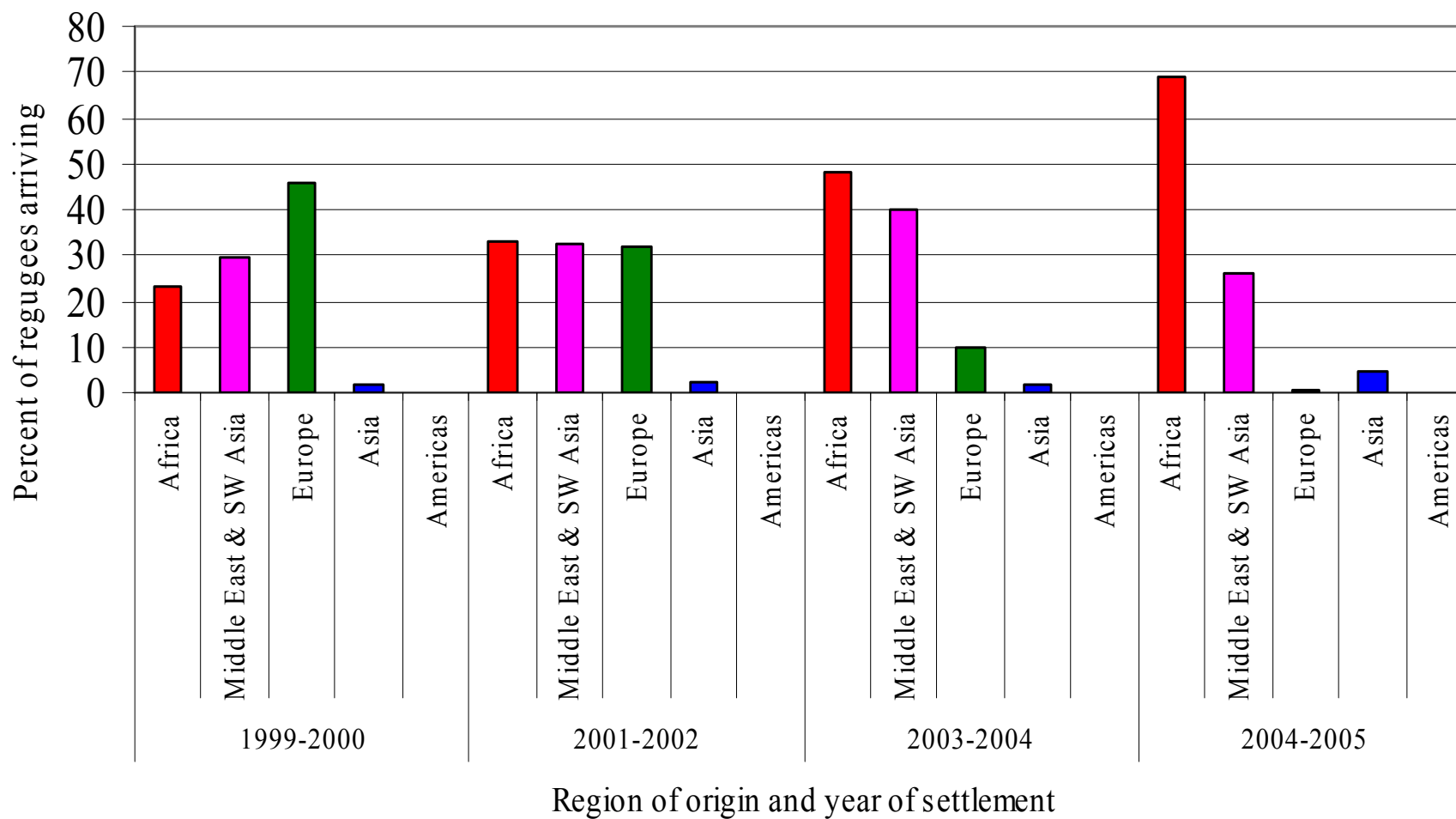
the  
children's  
hospital at Westmead

# Background

- Australia accepts approx 13 000 humanitarian entrants each year (40% children)
- 1000 refugee children <15 yrs old settle in NSW each year
  - most in metropolitan Sydney
- Health needs and poor access



# Australian Refugee intake by region



# Assessment

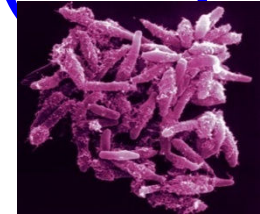


- Immunization status
- Mantoux or blood-based Interferon- $\gamma$  release assay (IGRA) = Quantiferon-TB gold
- CXR
- Bloods
  - FBC and Ferritin
  - Blood-borne viruses and serological evidence of other infections
  - “Rickets screen”  
(Calcium, Phosphorus, Alkaline phosphatase, 25 OHVit D, PTH)
- **SCREENING CONSENSUS?**



# Definitions – Tuberculosis (TB)

- **Past TB** – completed treatment
- **Active TB** – receiving treatment
- **Disseminated TB** – active TB affecting >1 organ system  
>1 region (e.g. multiple lymph node groups, multiple lobes of lung)
- **Latent TB infection (LTBI)** - either positive Mantoux (>10mm) or positive IGRA without evidence active TB or history treated TB
- **No TB** – negative Mantoux / IGRA and no clinical suspicion active TB



# Vitamin D-Master hormone

- Regulates
  - Immune function Macrophage activation
  - Restricts MTB growth *in vitro*
  - Initiates release of cathelicidin intracellular antibiotic
  - Before antibiotics Vit D used to treat TB
  
  - Darkly pigmented skin compared to fair skin needs 5-6 times longer sun exposure to make same amount Vit D
- Risk groups Vit D deficiency
  - African refugees via Egypt
  - Religious custom – Hejab, veil

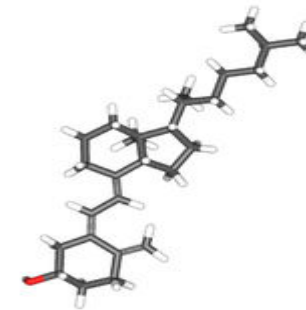


Image: Max Planck Institute for Infection Biology /Volker Brinkmann



## Deficiency definitions for Vit D (25OH Vit D)

<12.5 nmol/L	- Severe
12.5 - 25nmol/L	- Moderate
25 - 50nmol/L	- Mild deficiency
50 - 150nmol/L	- Sufficient



# What is known: TB and Vit D deficiency in Refugees

## – TB

- Active TB: approximately 0-1%
- LTBI: 25-55% in Australian clinics
- Less data for non-African refugees

## – Vit D deficiency

- 10% in NSW refugees
- 53% (<25nmol/l) in community audit in Victoria



## Vit D deficiency combined with TB

- Association of Vit D deficiency and TB
  - 155 refugee adults
    - Moderate Vit D deficiency ( $< 25\text{nmol/l}$ ) found in:
      - 78% active or past TB
      - 33% LTBI
      - Odds ratio for LTBI vs no TB = 8.0 (1.8-72.9)
  - UK refugee children with active or LTBI (n=64)
    - 37% Vit D deficient ( $< 20\text{nmol/l}$ )



# Aims

- To investigate:
  - Association between Vit D deficiency and TB in refugee children
  - To further characterise ALP and PTH levels



# Methods

- 291 children attending refugee clinic at CHW
- May 2005 to November 2008
  
- Mantoux test - positive  $\geq 10$  mm
- Routine "Rickets" screen
  - 25 OHD, ALP, PTH, Ca



# Methods

- BCG vaccination status confirmation:
  - BCG scar
  - Vaccination record card (rare)
  - Pre-2007 data - incomplete
- Vit D deficiency combined
  - Severe  $<12.5$  nmol/L
  - Moderate  $12.5 - \leq 25$  nmol/L



# Results

- n = 291
- Mantoux positive
  - n = 86 (30%)
    - 18% (n = 52) had Mantoux  $\geq$  15mm
    - 66% from Africa (Sudan = 35%)
- Vit D deficient
  - n = 62 (21%) ( $\leq$  25nmol/L)
    - 3.4% severe Vit D deficiency
- Mantoux positive and Vit D deficient
  - n = 25 (8.6%)



# Results

Variable	Mantoux negative	Mantoux positive	
<b>Number (%)</b>	205 (70%)	86 (30%)	
<b>Median age yrs (range)</b>	7.5 (0.5 –17.5)	8.7 (0.6 -17.7)	
<b>Male (%)</b>	110 (54%)	44 (51%)	
<b>Ethnic group</b>			
Black African	153 (75%)	53 (62%)	
Middle East	38 (19%)	26 (31%)	
Asia	6 (3%)	5 (6%)	
Other	6 (3%)	1 (1%)	
<b>Geometric mean Vit D nmol/L (95% CI)</b>	43.4 (40-47)	34.6 (30.9-38.8)	<b>p=0.001</b>
<b>Vit D deficient</b>			
<b>Mild</b> >25 -50 nmol/L(%)	76 (37%)	34 (40%)	
<b>Moderate</b> 12.5 -25 nmol/L(%)	<b>30 (15%)</b>	<b>22 (26%)</b>	<b>p=0.036</b>
<b>Severe</b> ≤ 12.5 nmol/L(%)	<b>7 (3%)</b>	<b>3 (3.5%)</b>	

## Results – BCG confirmed

- n= 93
- Mean age = 8.0 yrs (range 0.7-17.1)
- Mantoux positive
  - >10mm: n = 35 (38%)
    - ≥15 mm: n = 17
- Vit D deficient
  - 19%

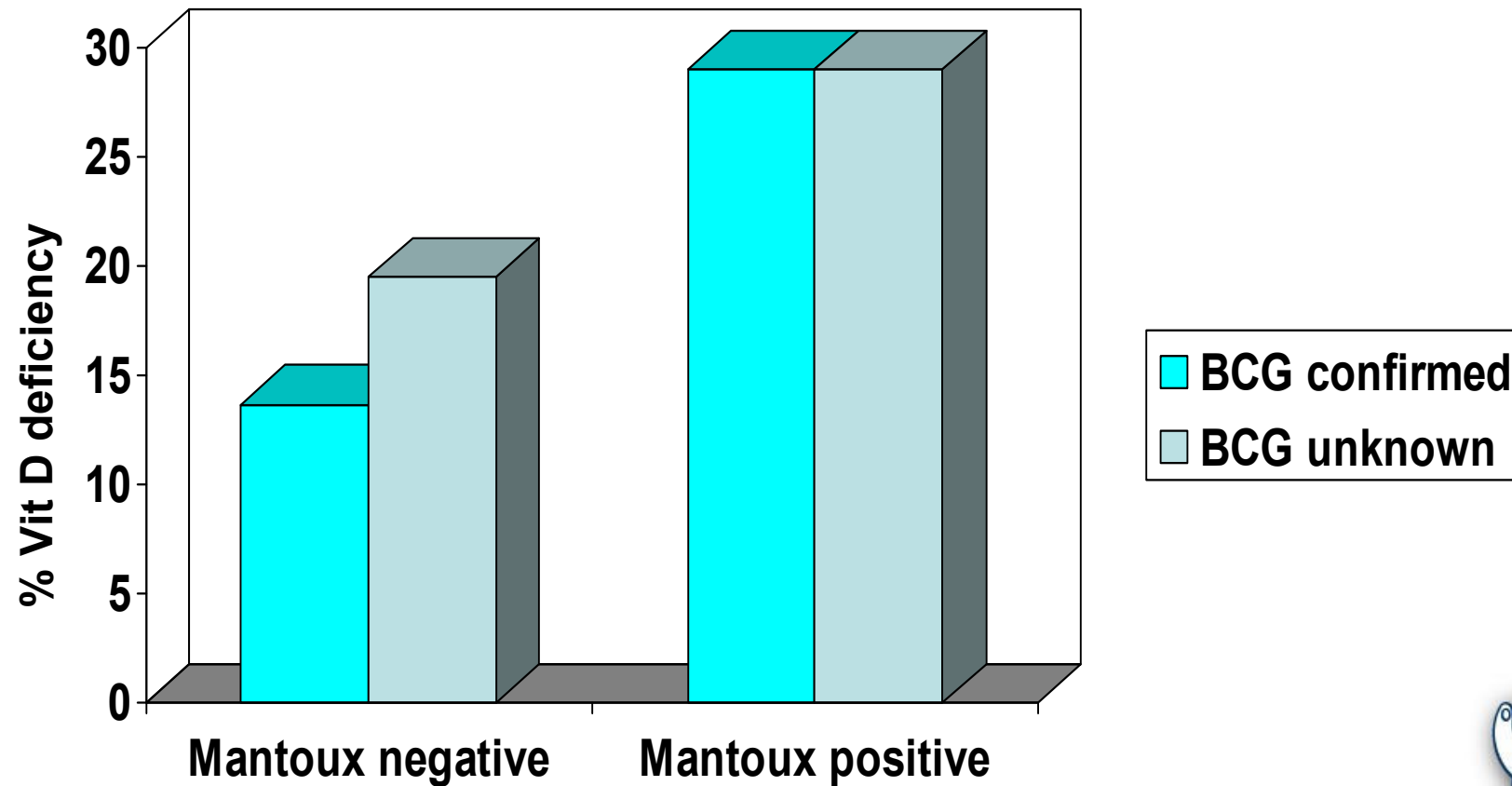


## BCG status and Mantoux and Vit D deficiency

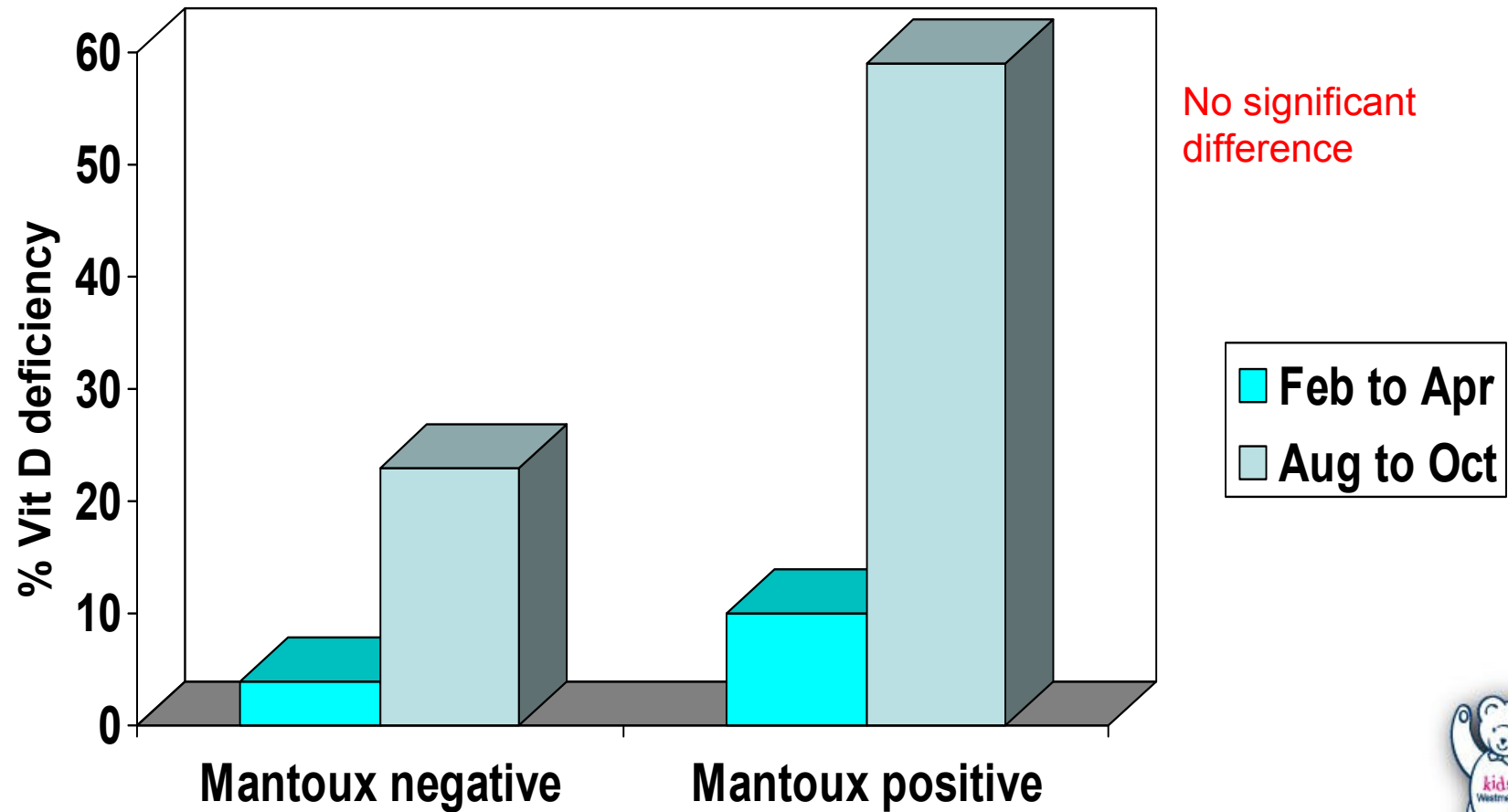
	BCG confirmed n=93	BCG unknown n = 198	
Mantoux positive	38%	26%	RR = 1.44 (1.03-2.01) p=0.03
Vit D deficient	19%	22%	p=0.15
Combined	10%	8%	p=0.37



# BCG and Vit D deficiency



# Season of testing and Vit D deficiency



## Ethnicity and Vit D deficiency

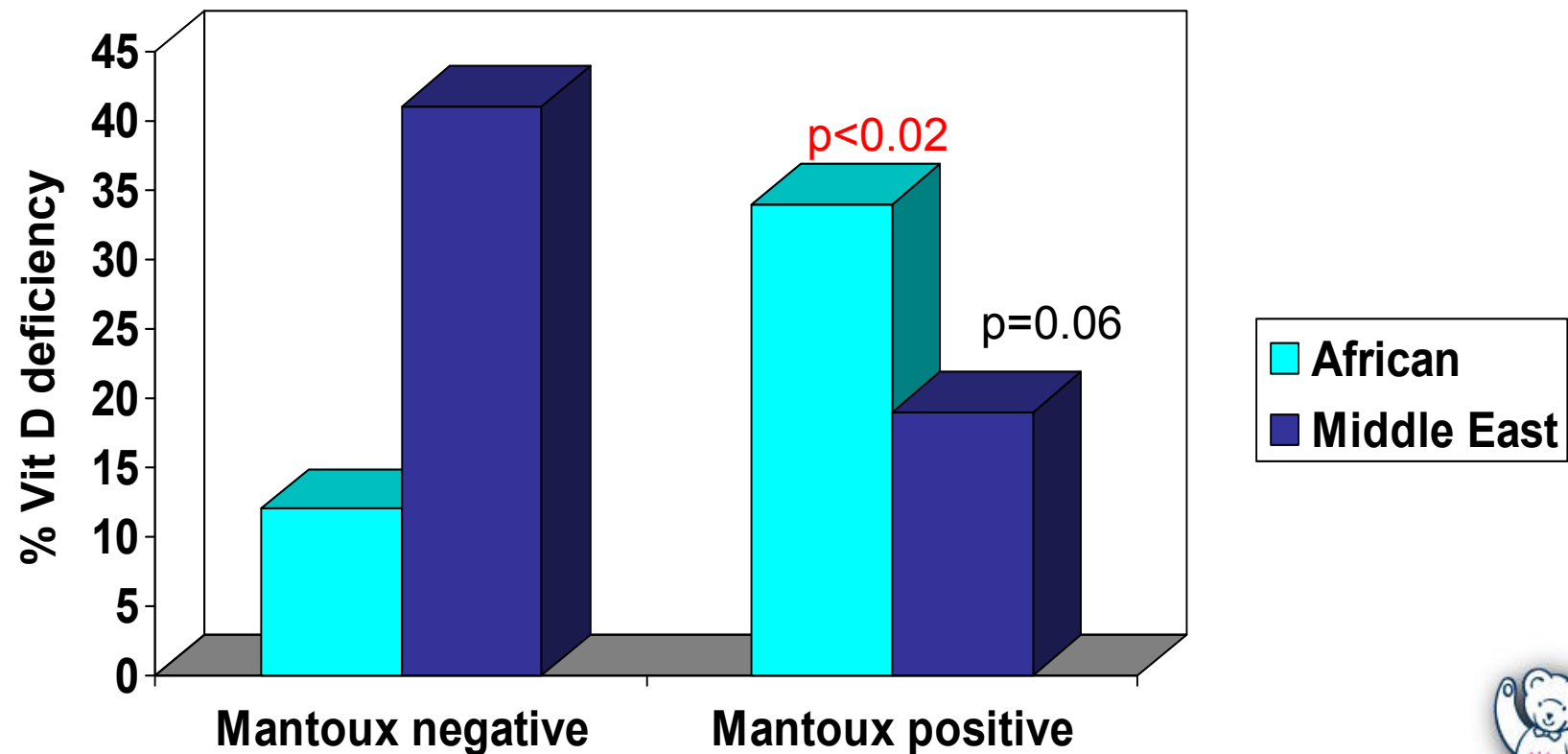
Ethnicity	Vitamin D < 25 nmol/L N (%)	Total
Africa	38 (18%)	207
Middle East	20 (30%)	66
Asia	1 (9%)	11
Other	3 (43%)	7
<b>Total</b>	<b>62 (21%)</b>	<b>291</b>

One third of middle east refugee children Vit D deficient

Nearly one fifth African refugee children Vit D deficient



# Ethnicity and Vit D deficiency



## Mantoux and other Vit D deficiency markers

	Mantoux negative	Mantoux positive
ALP (range)	293 (61-1138)	267 (49-608)
PTH (range)	7.2 (1-38.1)	6.9 (1-41.5)
Ca (range)	2.35 (1.56-2.66)	2.36 (1.69-2.53)

**No significant difference in ALP, PTH, Ca**



# Discussion

- 10% refugee children both Vit D deficient and LTBI
  - Confirmed BCG vs unknown BCG
  - no difference
- Significant association LTBI and Vit D deficiency in refugee children from
  - Sub-Saharan Africa
  - Not Middle East
  - Season of testing had no influence on this



# Association

- Vitamin D deficiency → TB
  - MTB predominately resides inside macrophages
  - Vit D enhances macrophage suppression of MTB growth
  - Lack of Vit D means reduced production of microbe killing cathelicidin
- TB → Vitamin D deficiency
  - MTB infection reduces vitamin D levels
  - Less evidence



# Conclusion

- Screening for one condition
  - Prompt assessment for other
  - Treat Vit D deficiency
- BCG history not complete
  - Needs further study
- Difference between African and Middle Eastern children



# Acknowledgements

- CHW refugee clinic and nursing staff
- Infection control nurses at CHW
- Refugee children and their parents





<http://www.asid.net.au>

**The Guidelines for diagnosis, management and prevention of infection in recently arrived refugees (March 2009)**

