

Vitamin D, does it help our children?

Dr. Cameron Grant FRACP PhD

Head of Department - Paediatrics: Child & Youth Health

Associate Professor in Paediatrics, the University of Auckland

Paediatrician, Starship Children's Health Park Road, Auckland,
New Zealand



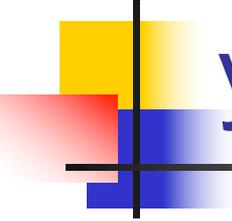
THE UNIVERSITY
OF AUCKLAND

NEW ZEALAND

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Te Whare Wānanga o Tāmaki Makaurau





At the end of this session you will be able to

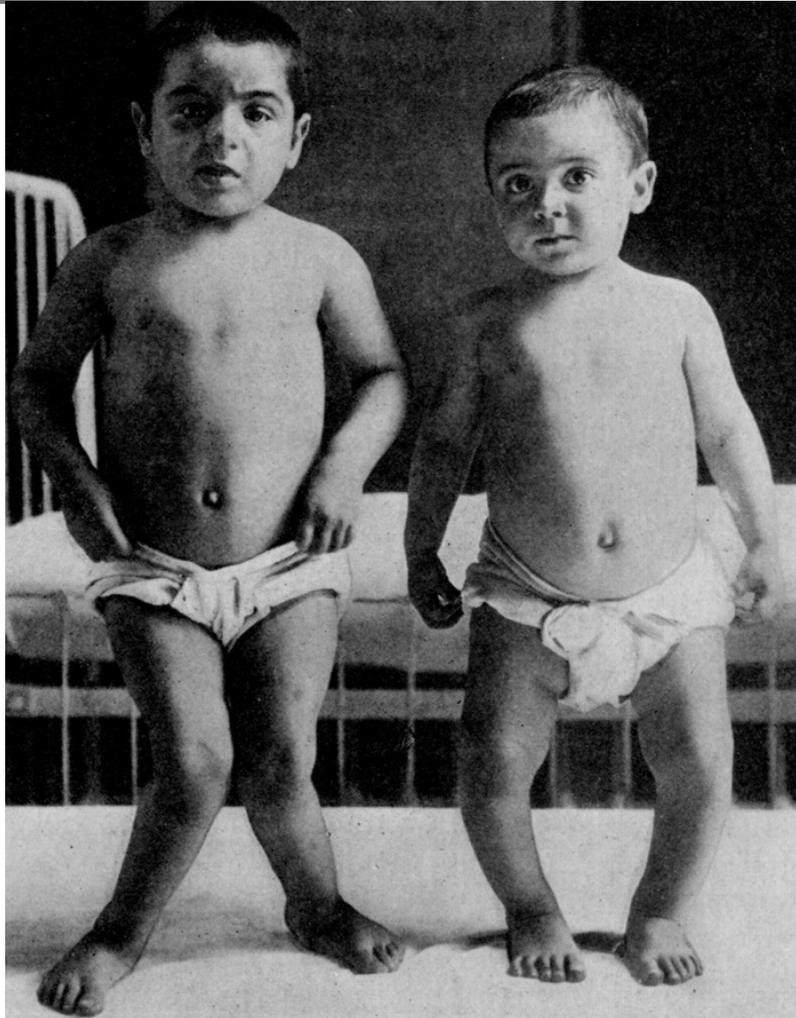
- Recognise that vitamin D deficiency during pregnancy and infancy is a global problem
- Understand why vitamin D status is poorer in New Zealand than in many other developed countries
- Demonstrate the potential for vitamin D status to be a determinant of respiratory health in early childhood

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Vitamin D deficiency causes rickets



Rickets in the 18th and 19th century before the industrial revolution

- A disease of the affluent
 - Style of clothing
 - Most of time indoors



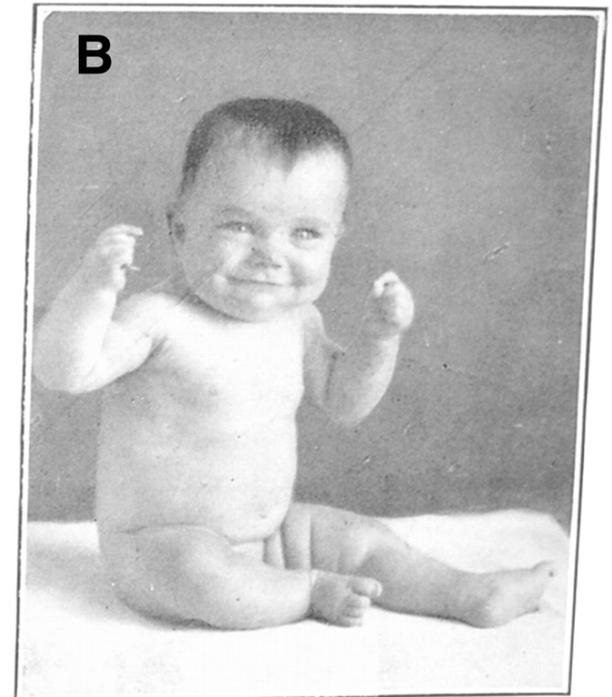
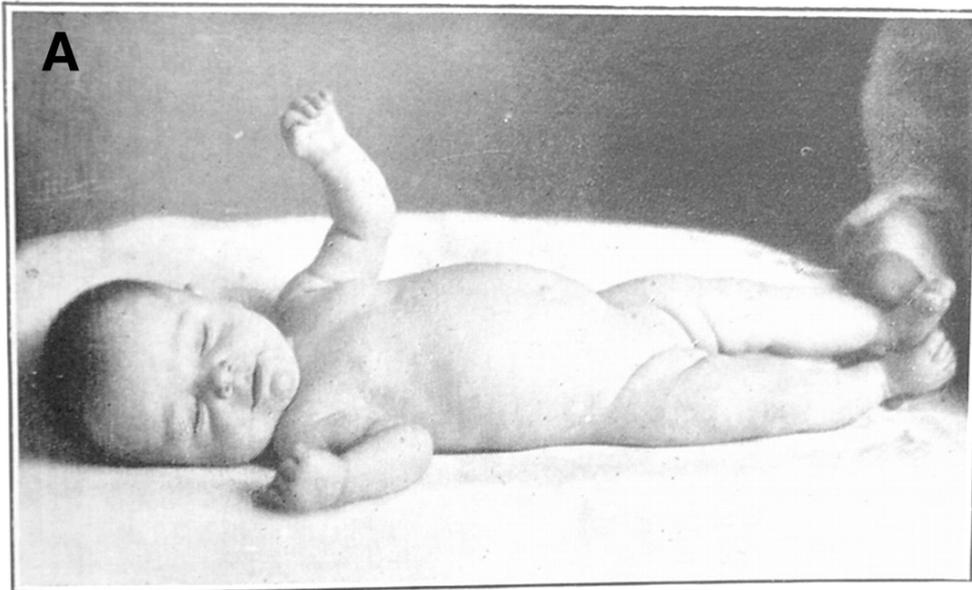
Rickets in the 19th century industrial revolution

Present in 50% of children in inner city neighbourhoods
UK/Europe/USA

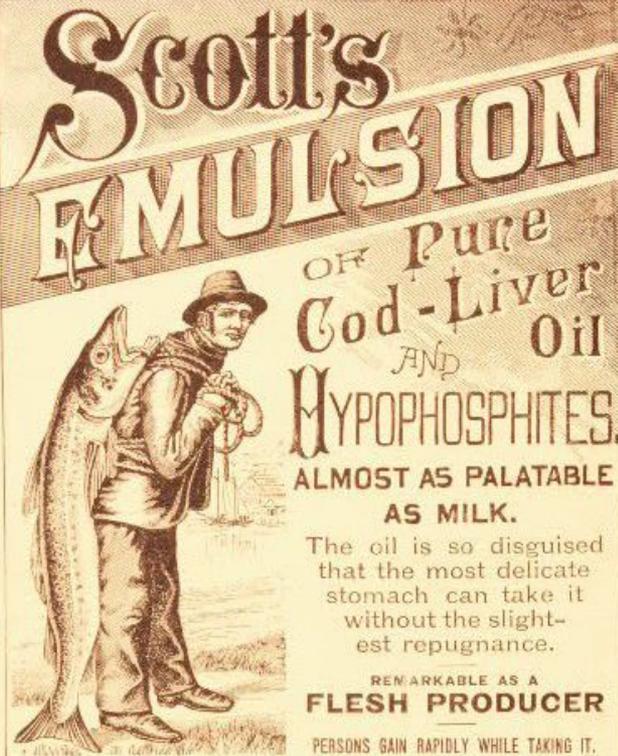


Garngad Slum, Glasgow, Scotland

Case H.G. in 1922 at age 8.5 months with rickets (A) and at 10 months after exposure outdoors, with rachitic lesions healed (B).



A major public health problem in 1900 to 1925 became a rarity



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OF Pure
Cod-Liver Oil
AND
HYPOPHOSPHITES.
ALMOST AS PALATABLE
AS MILK.

The oil is so disguised
that the most delicate
stomach can take it
without the slight-
est repugnance.

REMARKABLE AS A
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PERSONS GAIN RAPIDLY WHILE TAKING IT.

SCOTT'S EMULSION
Is acknowledged by numerous Physicians in the United States and many
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FOR THE RELIEF OF, AND IN MOST CASES A CURE FOR
**CONSUMPTION, SCROFULA, GENERAL DEBILITY, WASTING DISEASES
OF CHILDREN, AND CHRONIC COUGHS.**

For Sale by all Druggists. **SCOTT & BOWNE, New York.**



Rickets in children of specific groups of mothers 1960s to 1980s

- Indian & Pakistani women emigrated to England
- Muslim women in Middle east and Central Asia
- Religious groups in inner city north-eastern USA cities

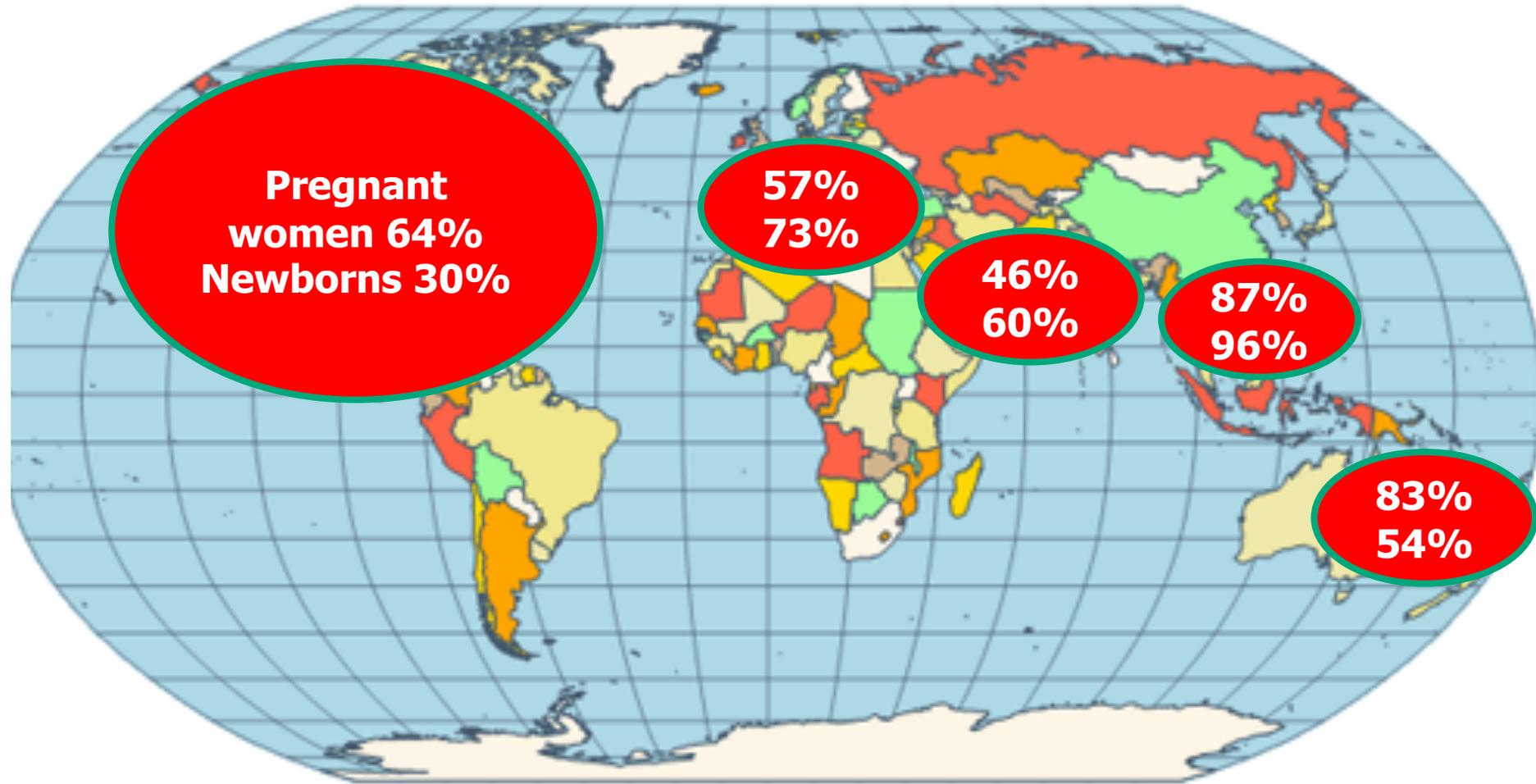


United States: Breastfed infants of African-American women 1990s

- Southern United States
- Exclusively breastfed
- Little time outside



Global prevalence of vitamin D deficiency* 1959-2014 in pregnant women and newborn infants



* As defined by a serum 25-hydroxyvitamin D (25OHD) concentration < 50 nmol/L

Recognise that vitamin D deficiency during pregnancy and infancy is a global problem

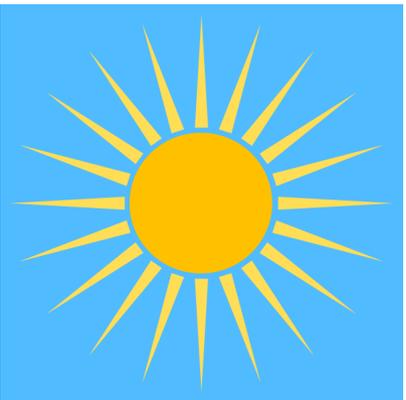
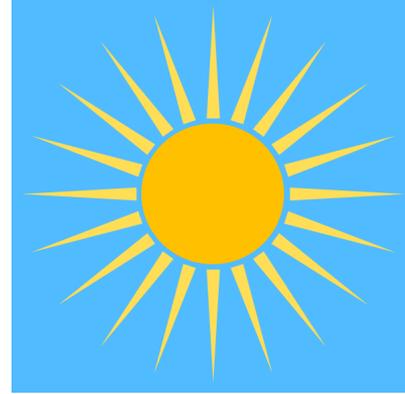
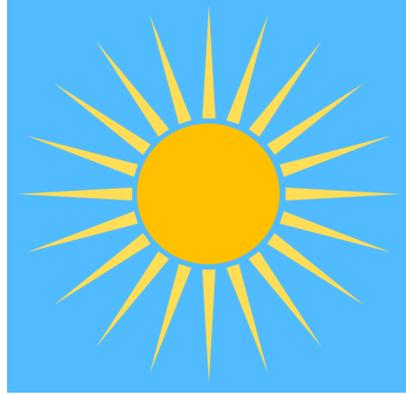
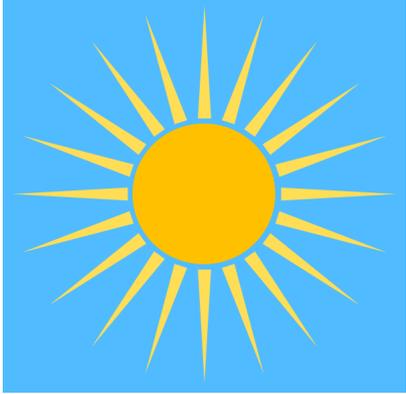


- Lifestyle patterns that interfere with our ability to make vitamin D result in vitamin D deficiency. Examples of this are evident from
 - 18th century
 - 19th century
 - 20th century
 - 21st century
- Vitamin D deficiency is a contemporary global public health issue

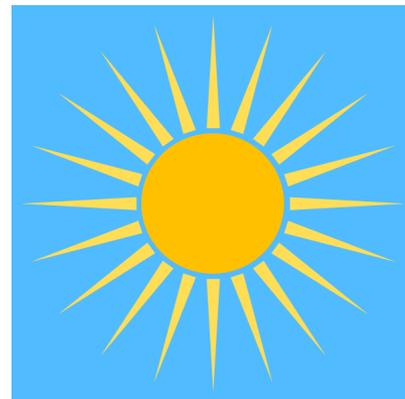
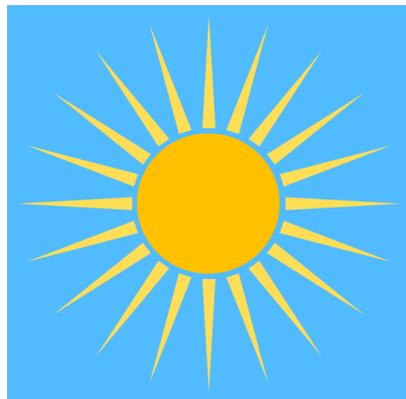
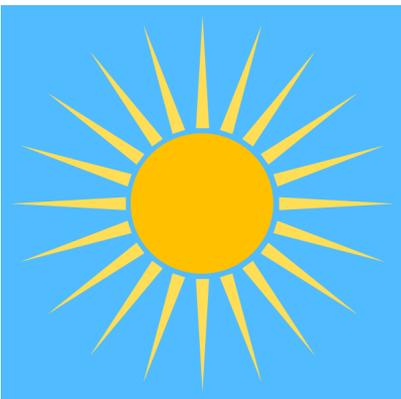
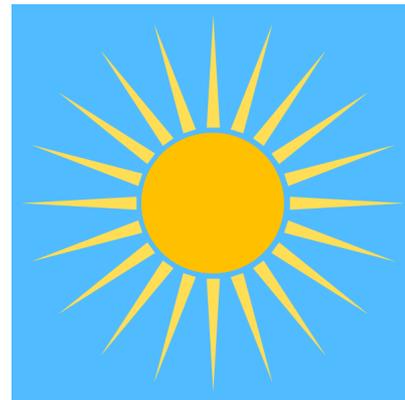
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90% of our
vitamin D
comes from
sunlight



Season variability in UV irradiation

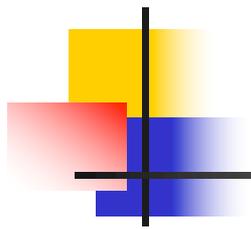


- Auckland 10 fold
- Invercargill 20 fold

In New Zealand it is very difficult to use sunlight safely



Sunscreen prevents vitamin D production in the skin



AOTEAROA

The land of the long white cloud

What happens below long white clouds?







Sunlight in Auckland

- Average of 4 hours per day of sunlight from May to August
- More rainy days per month than London, Birmingham or Edinburgh for 7 of the 12 calendar months



Other sources of vitamin D





"Bottled

Sunlight"

Extra rich in "sunshine vitamin" D. Possesses a fine, wholesome flavour.

115



Alfalfa



Portabella mushrooms

**Shiitake
mushrooms**



Vitamin D dietary sources in the USA

Vitamin D dietary sources in New Zealand

Vitamin D



The body itself makes vitamin D when it is exposed to the sun

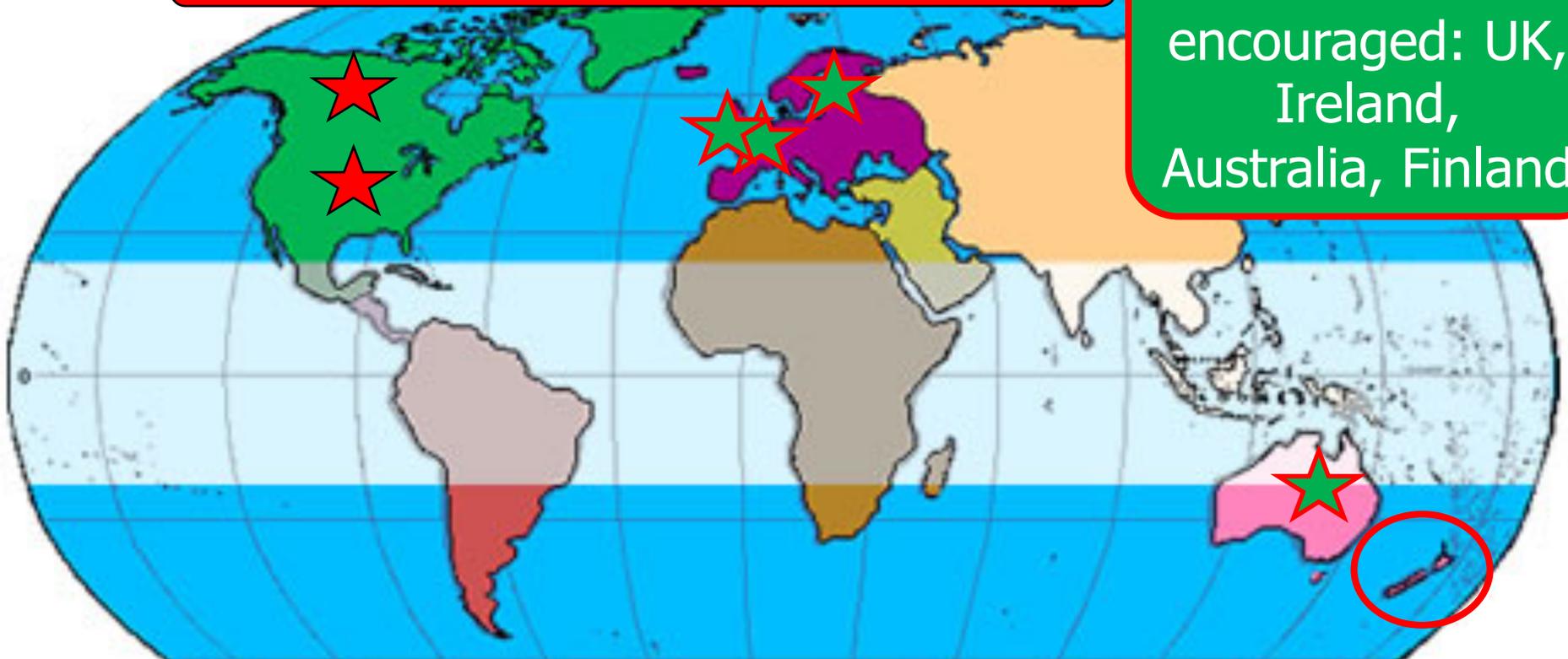
~~Cheese, butter, margarine, fortified milk, fish and fortified cereals are food sources of vitamin D~~



Fortification of food with vitamin D

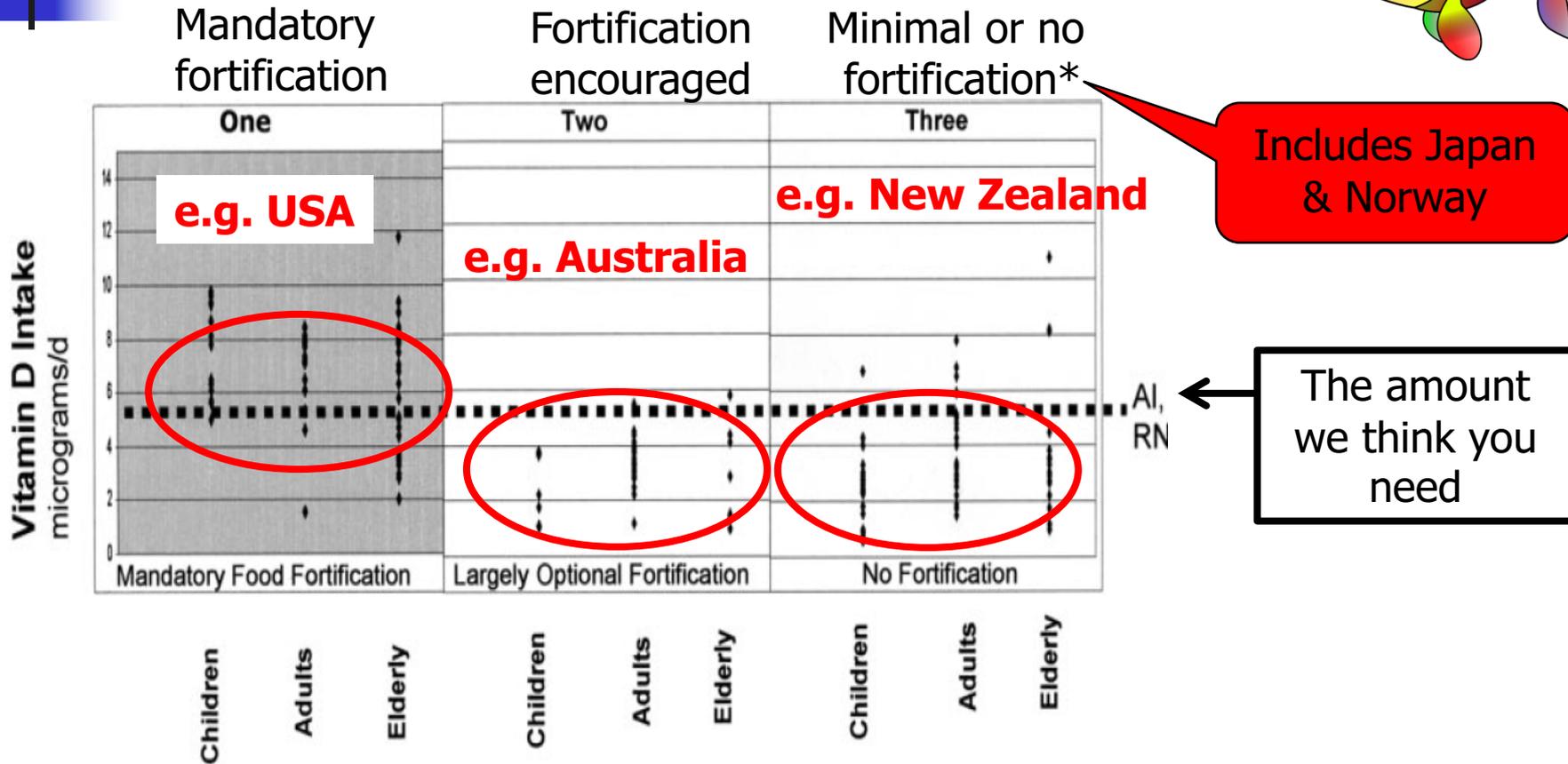
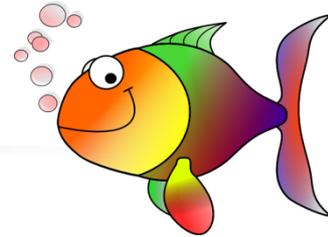
Mandatory fortification: Canada, USA

Fortification encouraged: UK, Ireland, Australia, Finland



No mandatory fortification and limited use of optional fortification: all other countries including New Zealand

Global vitamin D status

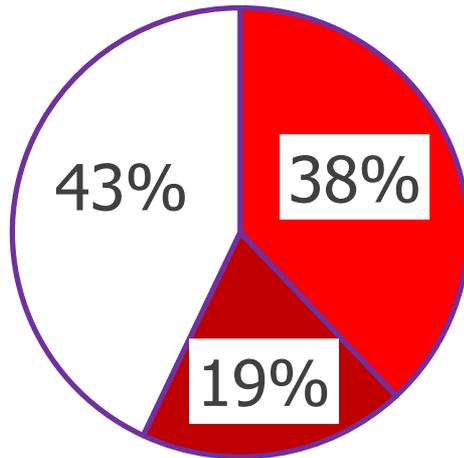


Vitamin D deficiency is prevalent in young New Zealand children

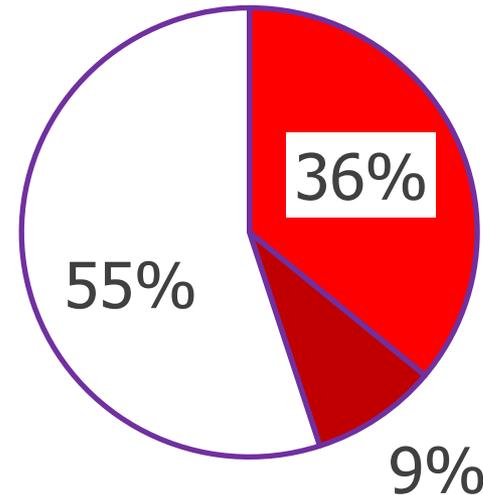


**Newborns in New Zealand
(Christchurch and Wellington)**

**6 to 23 month olds in NZ
(Auckland)**

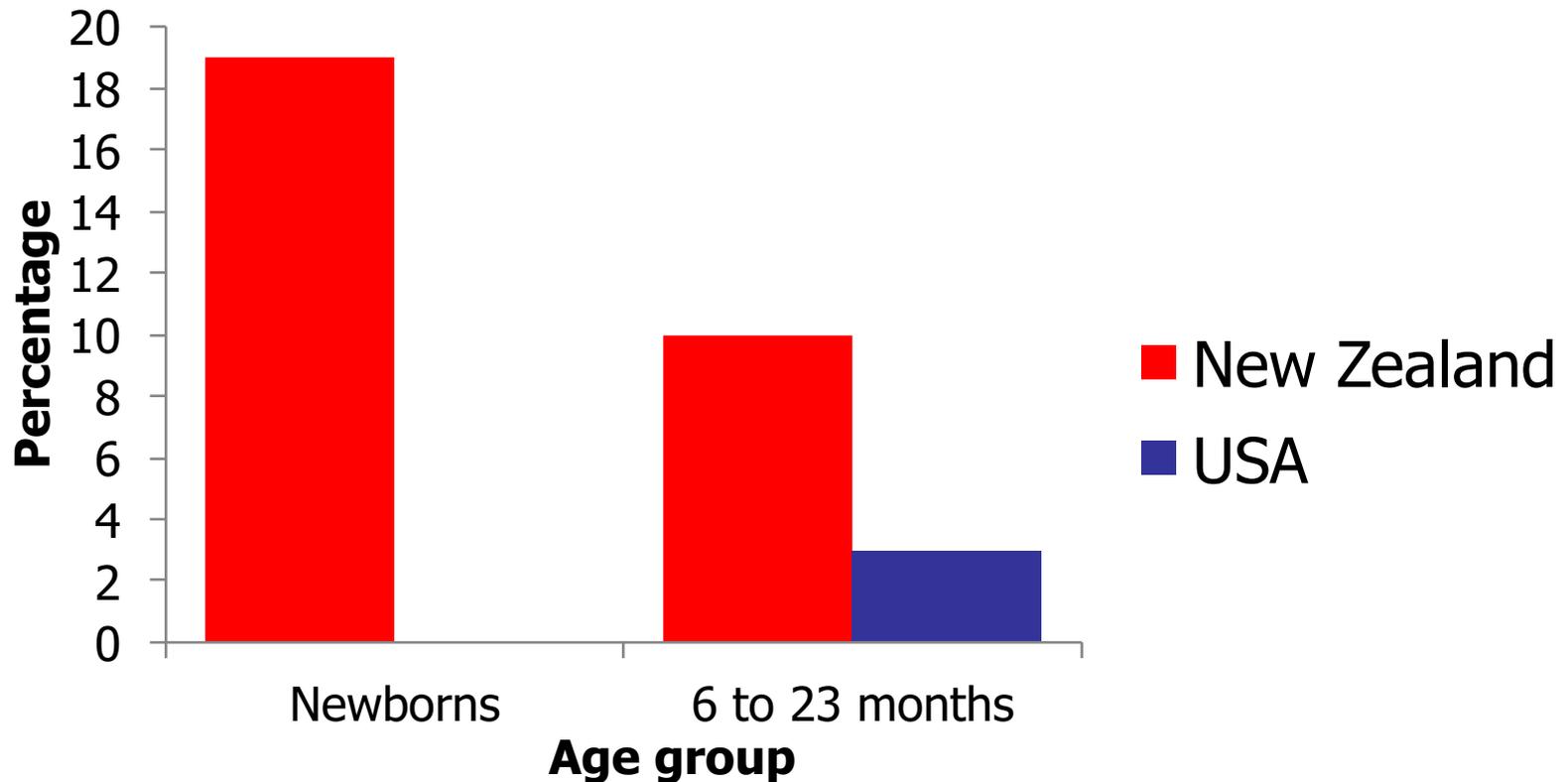


- Vitamin D deficiency*
- Severe vitamin D deficiency**
- Normal vitamin D



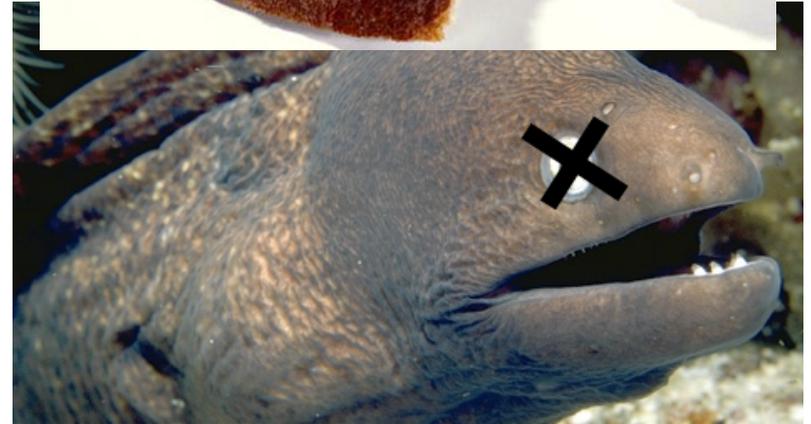
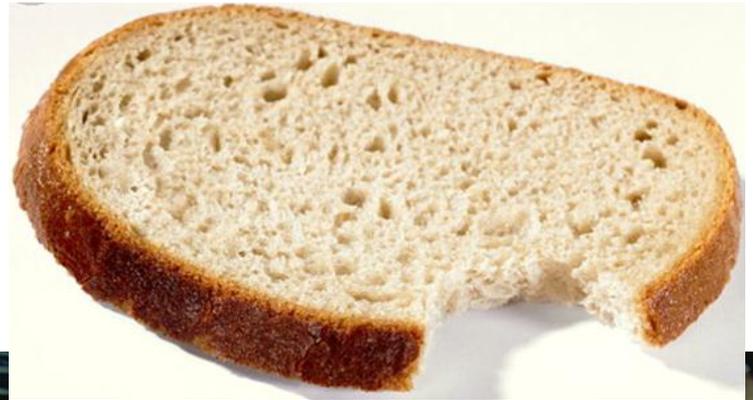
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What proportion of young children are at risk of rickets in New Zealand?

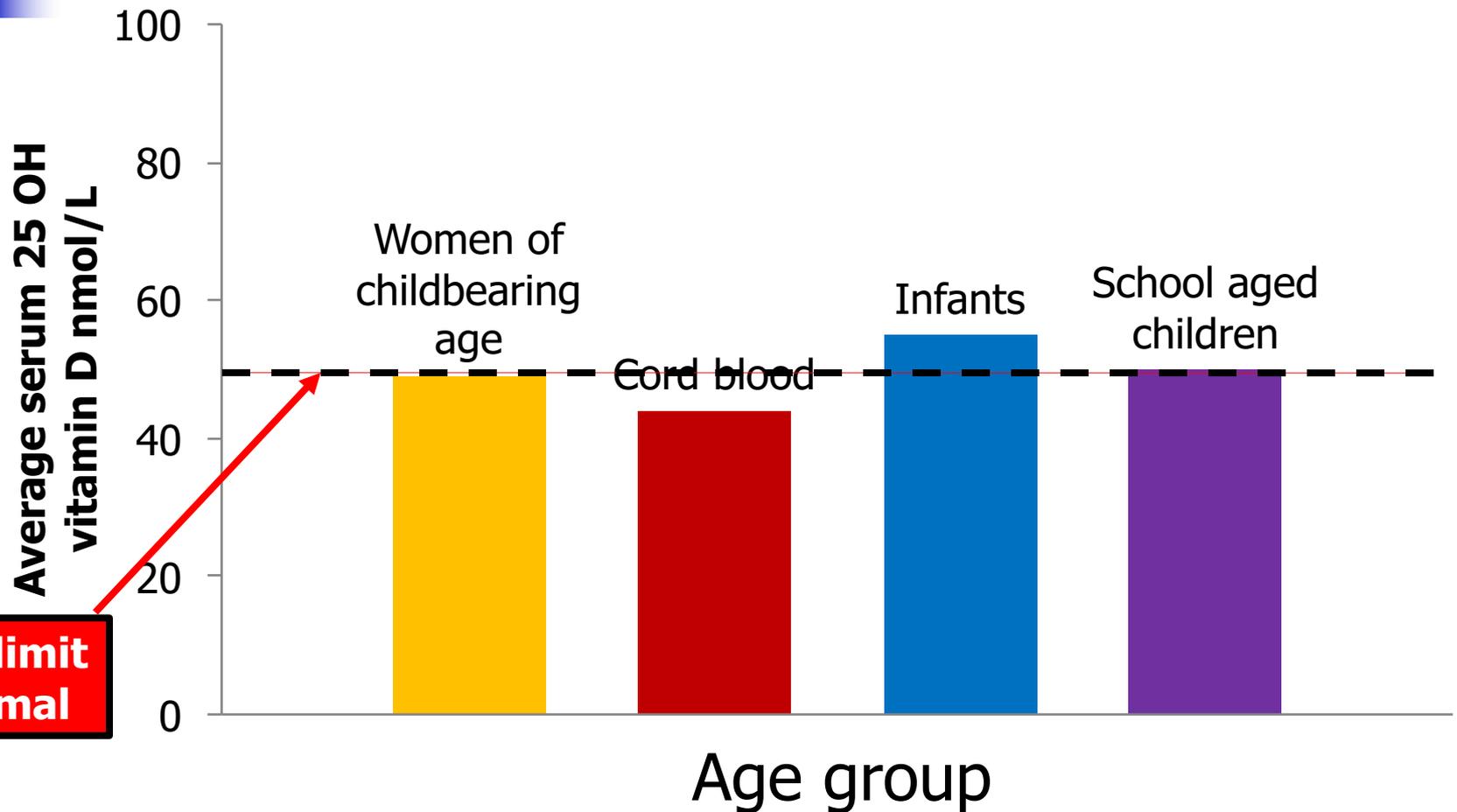


Peak incidence of rickets is between 3 and 18 months of age

**Its easy, all you
need to do is feed
me more oily fish
and liver
sandwiches**



Vitamin D status in New Zealand across the age range



Understand why vitamin D status is poorer in New Zealand than in many other developed countries



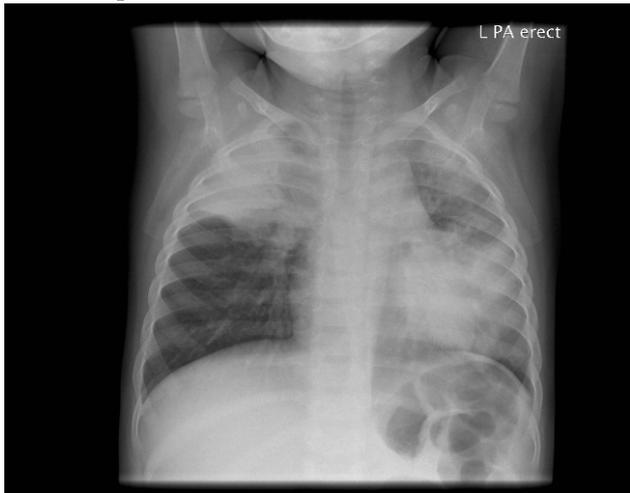
- NZ lies entirely below the Tropic of Capricorn
- Sun avoidance health policy
 - Not equally appropriate for all ethnic groups
- Large seasonal variation in sunlight
- Few foods are fortified with vitamin D
- Vitamin D supplementation is not routinely recommended

At the end of this session you will be able to



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Nutritional rickets and pneumonia



- Pneumonia is more frequent in children with rickets (Middle East)¹
- Children < 5 years old nutritional rickets associated with increased risk of pneumonia & hospital admission with lower respiratory tract infection (Middle East, Africa)^{2,3}
- Among hospitalised children rickets is associated with an increased risk of death from lower respiratory tract infections and specifically from pneumonia (Middle East)^{4, 5}
- Subclinical vitamin D deficiency risk factor for severe acute lower respiratory tract infections in children in India⁶

1. Salimpour R. *Arch Dis Child* 1975;50:63-6.

2. Muhe L, et al. *Lancet* 1997;349:1801-4.

3. Najada AS, et al. *J Trop Pediatr* 2004;50:364-8.

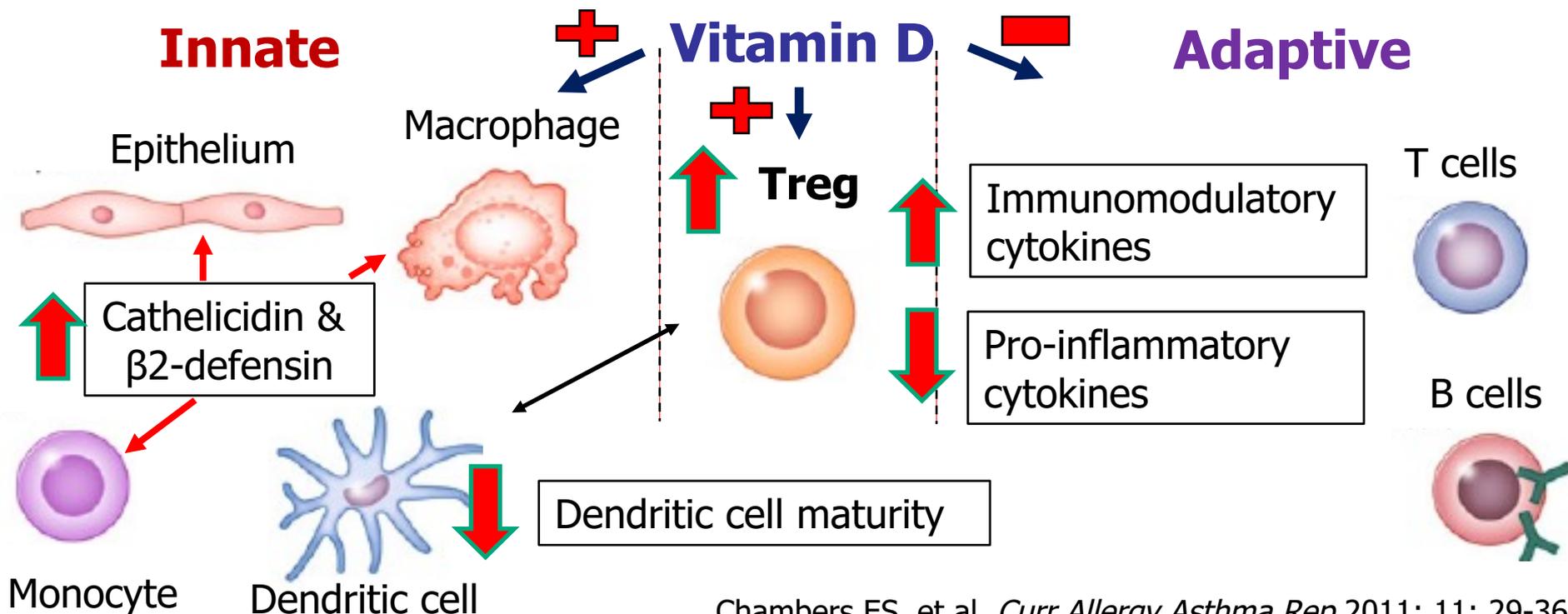
4. Banajeh SM. *J Trop Pediatr* 1998;44:343-6. ■

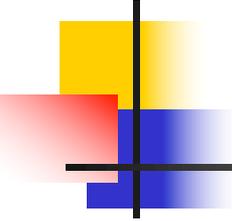
5. Banajeh SM, et al. *Ann Trop Paediatr* 1997;17:321-6.

6. Wayse V et al. *Eur J Clin Nutr* 2004;58:563-7.

Vitamin D is a modulator of the immune system

Vitamin D has effects on cells of the innate and adaptive immune response that maintain innate immune mechanisms necessary for defence against infection while promoting peripheral tolerance

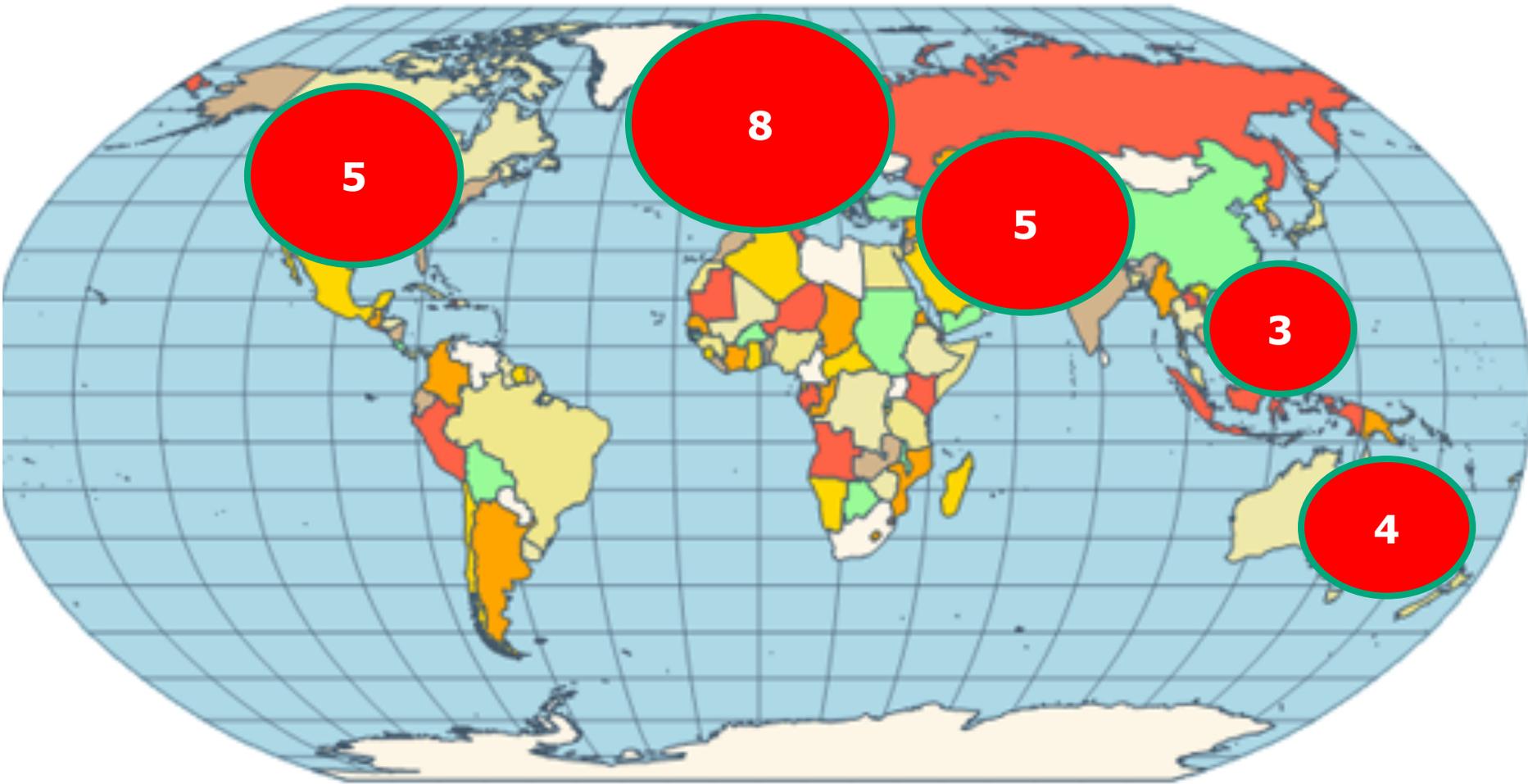




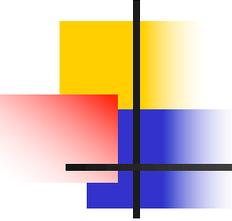
What is the clinical trial evidence that vitamin D prevents acute respiratory infections?

- Individual patient level meta-analysis of 25 clinical trials
- 25 eligible randomised controlled trials
- 11,321 participants
- Aged 0 to 95 years

Number of clinical trials by global region that have determined whether vitamin D supplementation protects against acute respirator infections



Martineau AR, Jolliffe DA, Hooper RL, et al. Protective effects of vitamin D supplementation against acute respiratory infection are greatest in those with the lowest baseline vitamin D status. European Respiratory Society 2016 International Conference. London; 2016.



Protective effects of vitamin D supplementation against ARI modified by baseline vitamin D status

- Modest protective effect for everyone
 - Adjusted odds ratio 0.86, 95% confidence intervals 0.79 to 0.95
- Strong protective effect among those with baseline 25-hydroxyvitamin D < 25 nmol/L.
 - Adjusted odds ratio 0.55, 95% confidence intervals 0.40-0.75
- No protective effect if large bolus doses used

What about in the New Zealand context?



The two New Zealand placebo-controlled trials of vitamin D supplementation and prevention of acute respiratory infections

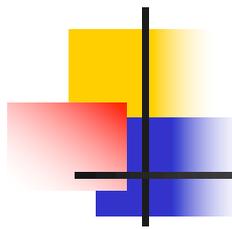
Murdoch et al 2012

- 322 healthy adults \geq 18 years old
- Staff or students of Canterbury District Health Board
- Ethnicity
 - 95% European
- Vitamin D 200,000 IU then monthly doses of 100,000 IU for 18 months

Grant et al 2015

- 260 healthy pregnant women attending a maternity care clinic in Manukau City
- And then their infants
- Ethnicity
 - 37% Pacific
 - 18% Māori
 - 19% Asian
 - 26% European
- Two dosing regimes

Pregnant women, from enrolment at 27 weeks gestation to birth, and then their infants, from birth to age 6 months, were randomly and equally assigned, to one of three groups



Mother from 27 weeks gestation until child is born

Infant from birth to age 6 months

Vitamin D₃
2000 IU/day

Vitamin D₃
800 IU/day

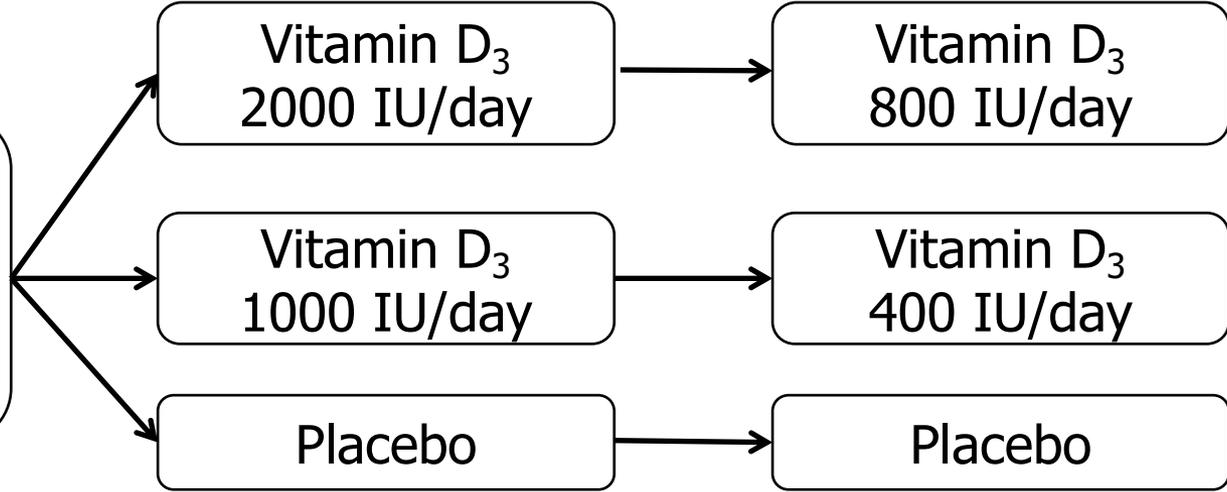
Vitamin D₃
1000 IU/day

Vitamin D₃
400 IU/day

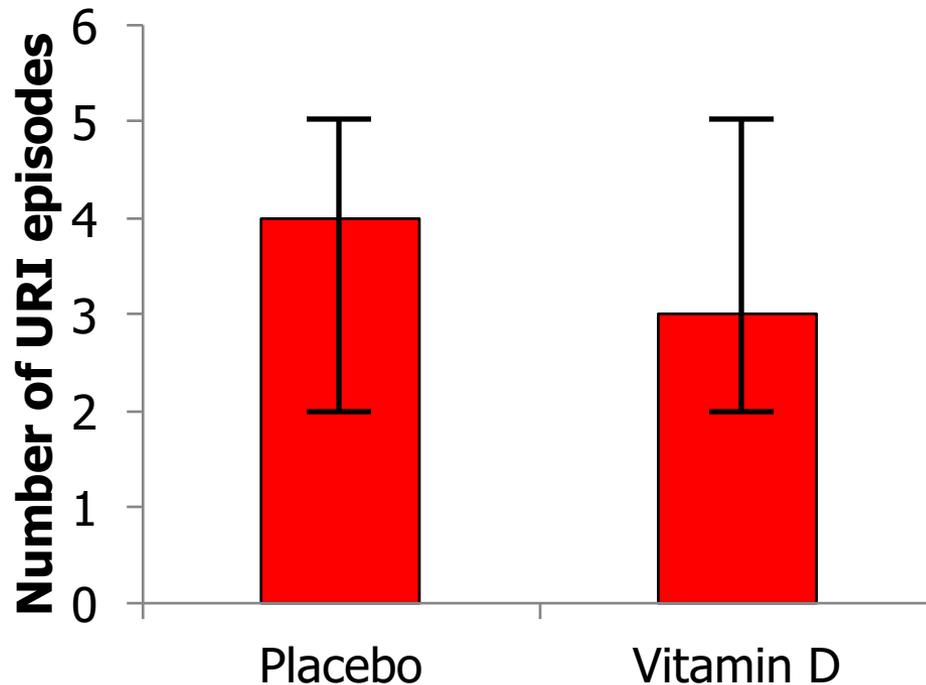
Placebo

Placebo

Enrolment & randomisation at 27 weeks gestation

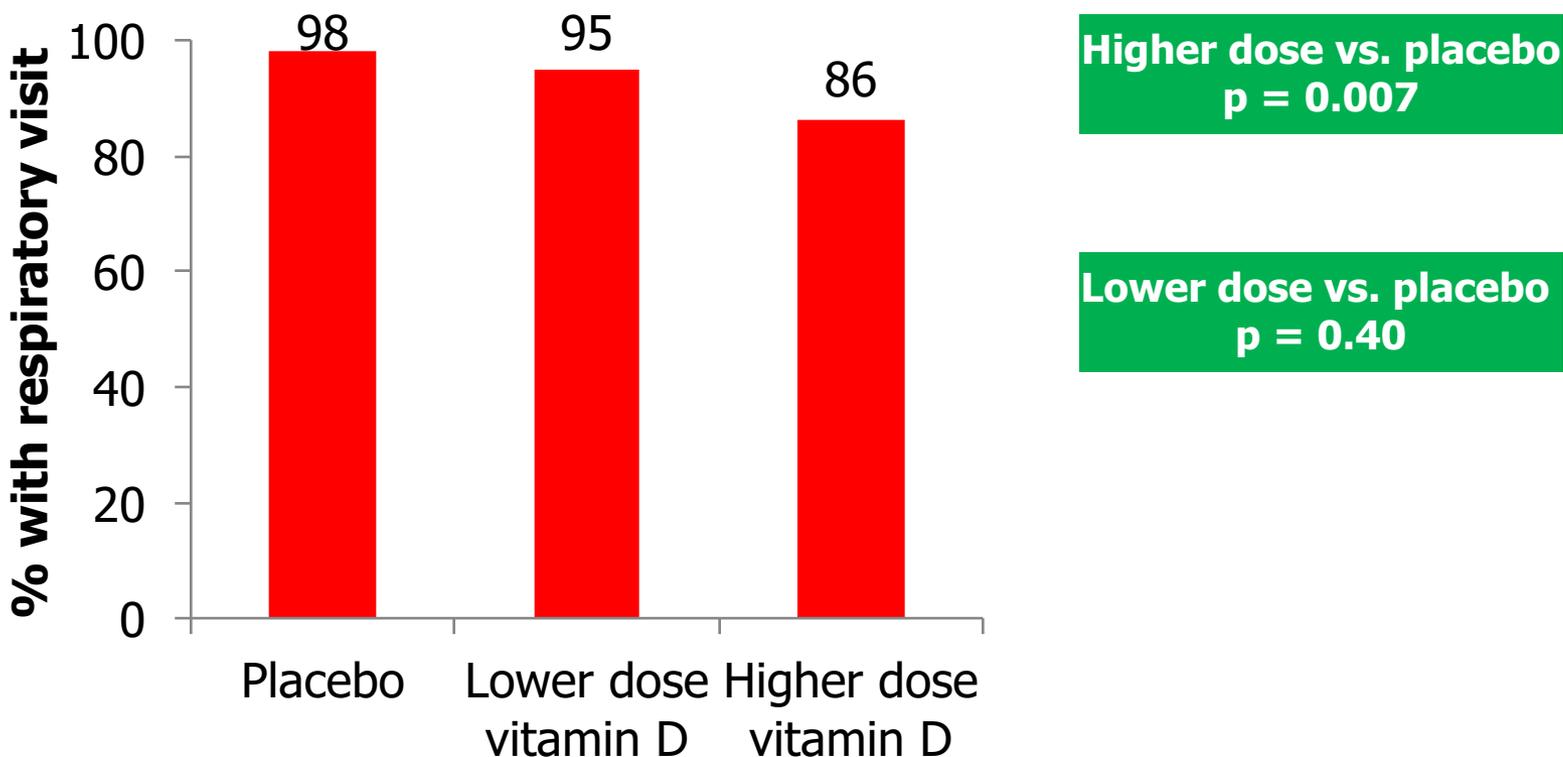


Median number of self-reported upper respiratory tract infection episodes per person



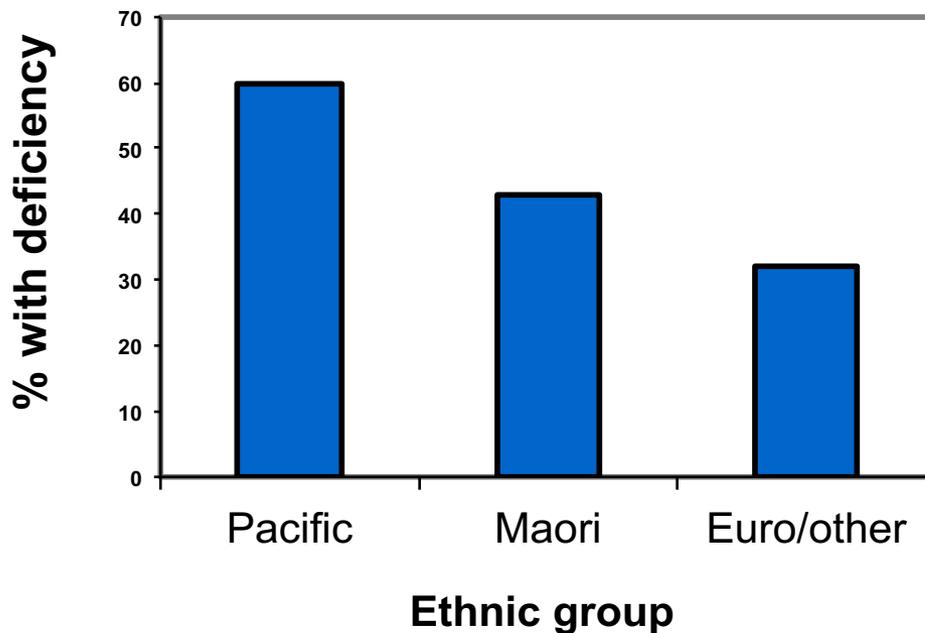
Vitamin D vs. placebo
 $p = 0.82$

Percentage of children making primary care visits for respiratory infections determined by audit of primary care records

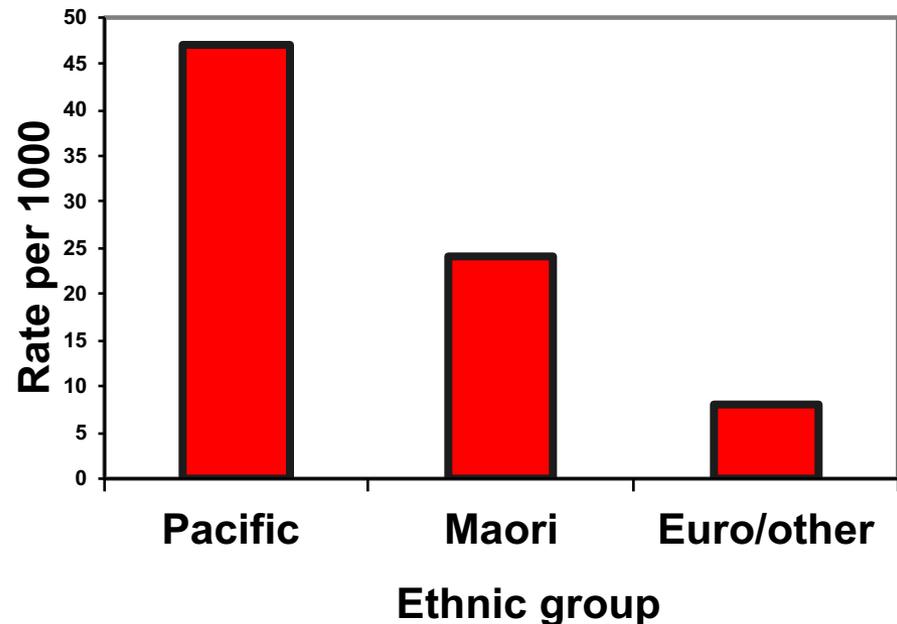


So for whom in New Zealand is vitamin D supplementation most likely to be an effective preventative strategy?

■ Vitamin D children 6-23 months



■ Pneumonia hospital admission rate Auckland age < 2 years



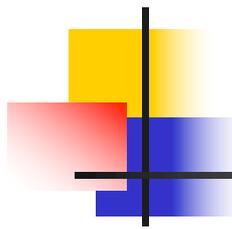
Grant CC et al. J Paediatr Child Health 1998;34:355-9.

Grant CC, Wall CR, Crengle S, Scragg R. Pub Health Nutr 2009; 12(10):1893-901.

And what about asthma?



Pregnant women, from enrolment at 27 weeks gestation to birth, and then their infants, from birth to age 6 months, were randomly and equally assigned, to one of three groups



Mother from 27 weeks gestation until child is born

Infant from birth to age 6 months

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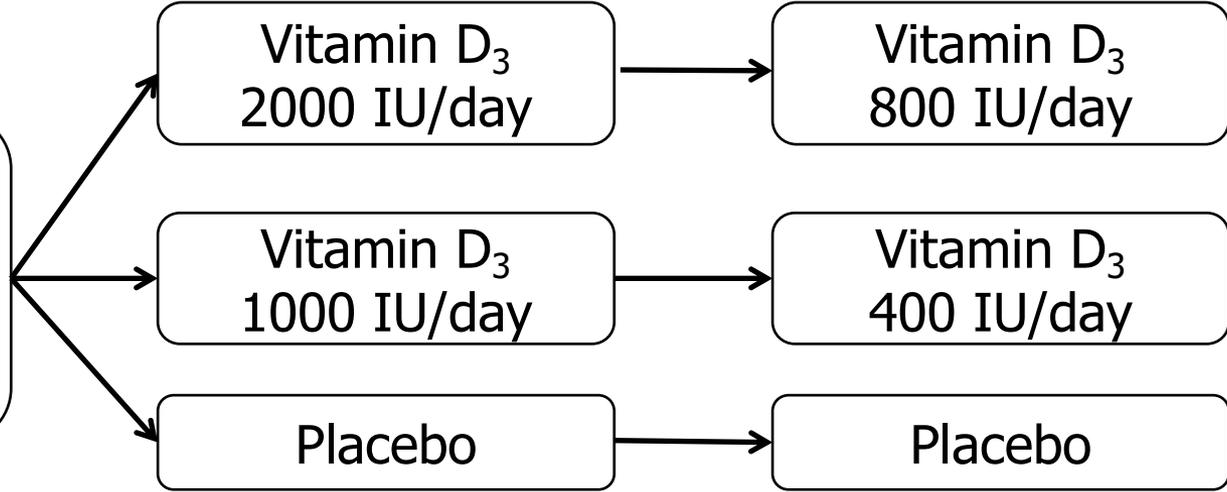
Vitamin D₃
1000 IU/day

Vitamin D₃
400 IU/day

Placebo

Placebo

Enrolment & randomisation at 27 weeks gestation



Measurement of aeroallergen sensitisation which the children were aged 18 months

■ Skin prick testing

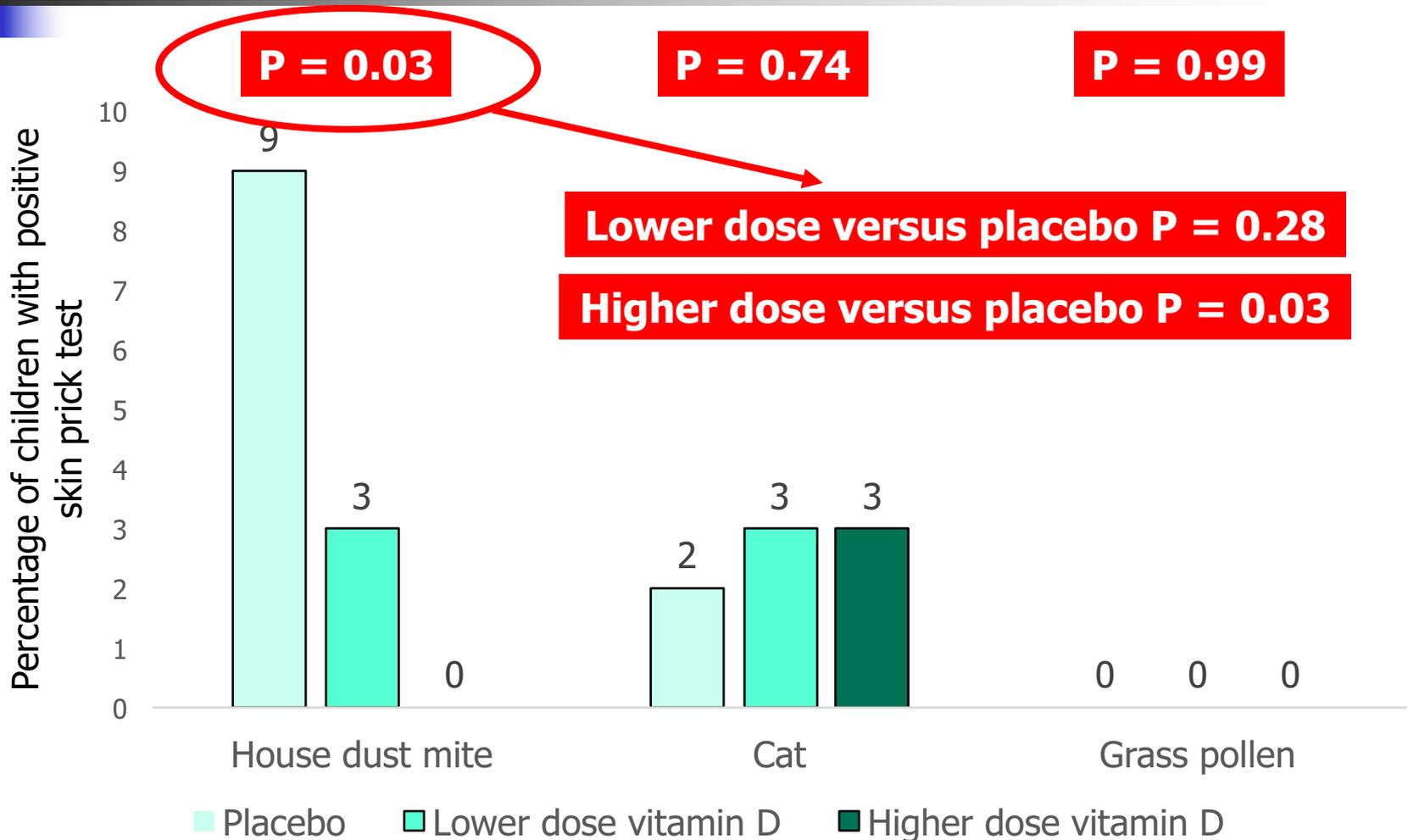
- House dust mite, cat and pollen
- Positive response = wheal diameter at least 3mm greater than the negative control

■ Specific serum IgE

- Semi-quantitative measurement (ImmunoCAP, Pharmacia, Uppsala, Sweden)
- Animal; Polcalcin; Grass, Tree and weed pollens; Mould; Mites; and Cockroach
- IgE responses categorised as
 - Undetectable (ISAC Standardized Units (ISU) 0-0.3)
 - Low (ISU >0.3-1.0)
 - Moderate/high (ISU >1-15)
 - Very high (ISU >15)



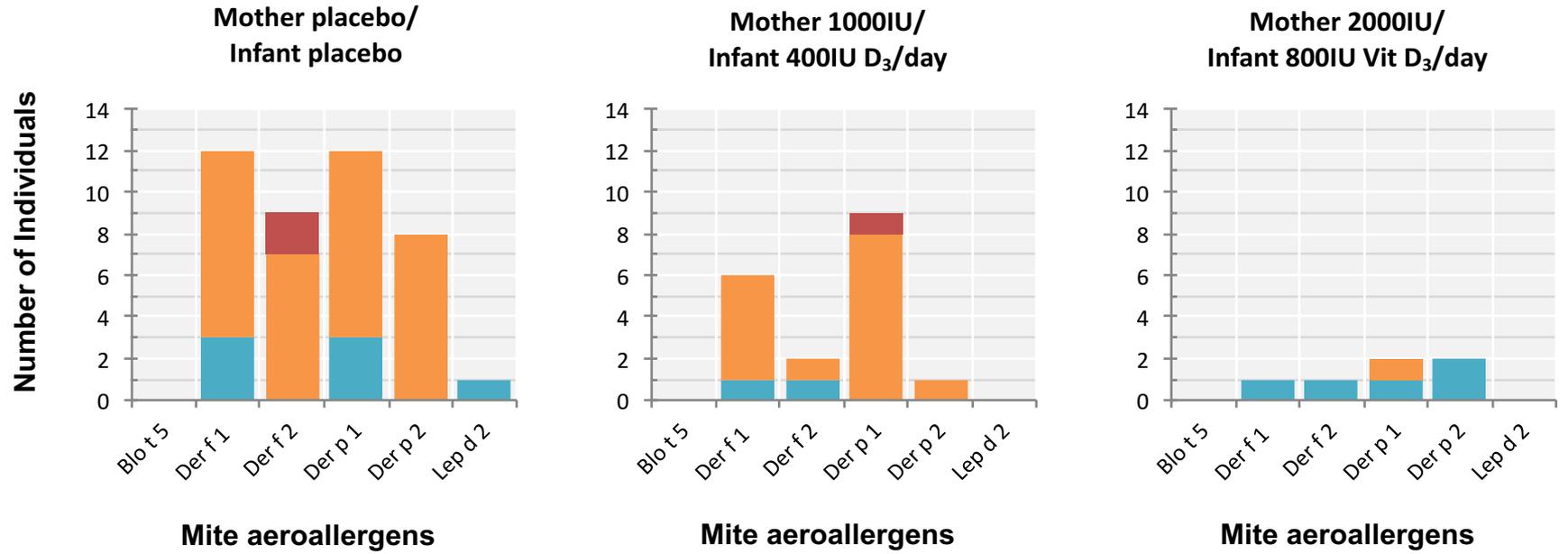
Positive skin prick test results at age 18 months in children randomly assigned to placebo, lower dose, or higher-dose vitamin D supplementation from 27 weeks gestation to age 6 months



Quantification of serum specific IgE response to mite antigens by study group: placebo, lower dose vitamin D₃, higher dose vitamin D₃.

Der f = *Dermatophagoides farinae*
 Der p = *D. pteronyssinus*

Response to Challenge
 Low Moderate/High Very High
 Blot = Blomia
 Lepd = Lepidog



IgE responses varied between study groups to the mite antigens Der f1 (p=0.01), Der f2 (p=0.004), Der p1 (p=0.02) and Der p2 (p=0.001)

Lower dose vs. placebo: Der f2 (P=0.03), Der p2 (P=0.03)

Higher dose vs. placebo: Der f1 (P=0.002), Der f2 (P=0.009), Der p1 (P=0.01) Der p2 (P=0.004)

Abstraction and coding of primary care visit data to age 18 months

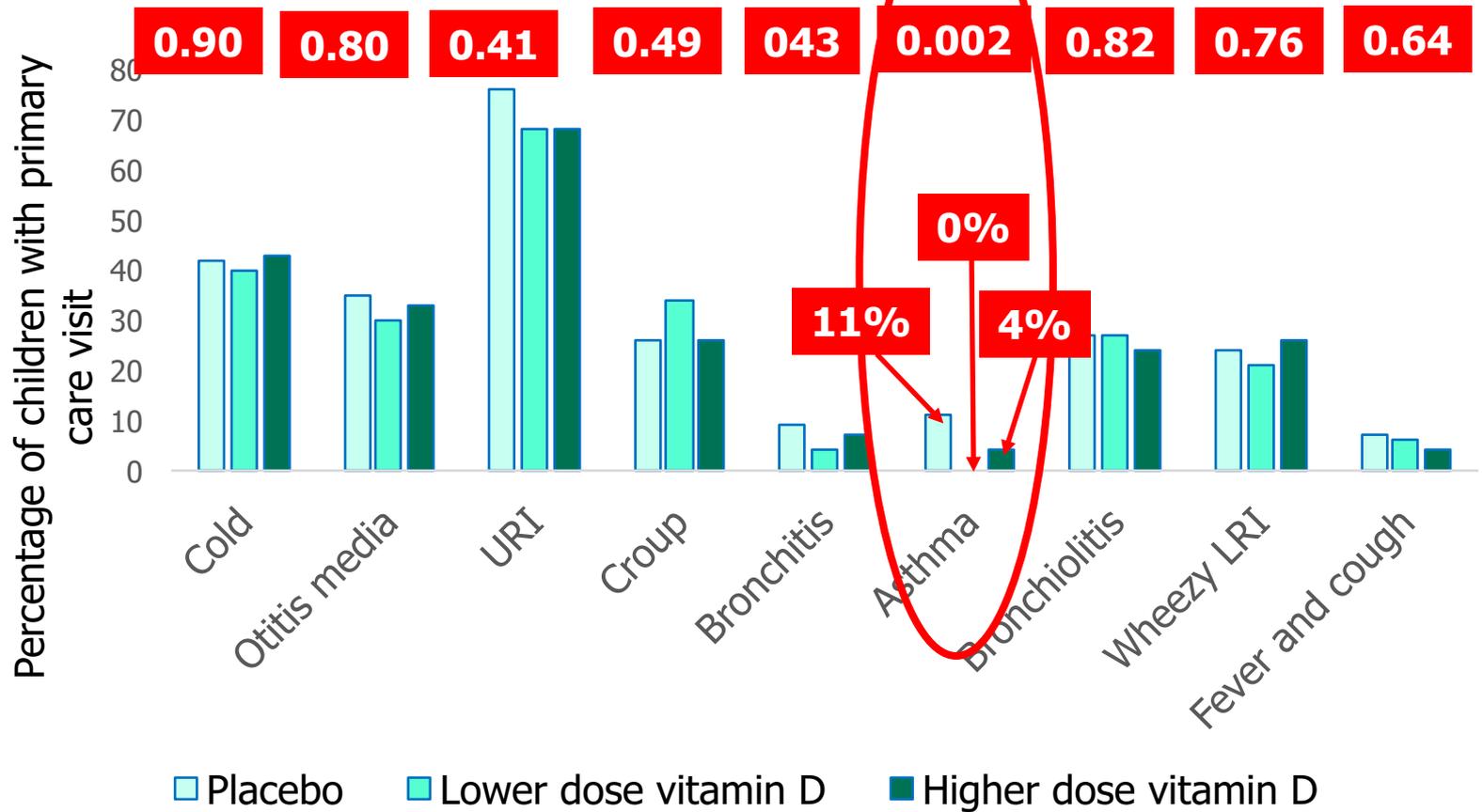
- Primary care records contained free text descriptions of diagnosis & management
- Primary care doctor visits coded as
 - Acute care
 - Well child care
 - Other e.g. follow up to check on illness resolution

Acute care visits for respiratory illnesses grouped as:

- Cold or influenza, otitis media, upper respiratory infection, croup, bronchitis, asthma, bronchiolitis, wheezy lower respiratory infection, fever + cough



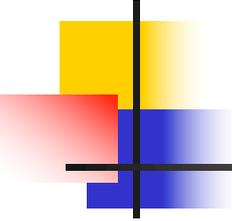
Number of children with an acute primary care respiratory illness visit up to age 18 months by doctor diagnosis



Lower dose vs. placebo P = 0.003

Higher dose vs. placebo P = 0.03

Vitamin D and asthma exacerbations



- Systematic review and meta-analysis
- 5 randomised controlled trials in primary school aged children with asthma in Denmark, Japan, Poland, United States and India
- Daily dose from 500 to 2000 IU
- Reduction in asthma exacerbations
- Risk ratio 0.41, 95% CI 0.27-0.63

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- **Demonstrate the potential for vitamin D status to be a determinant of respiratory health in early childhood**

The potential for vitamin D status to be a determinant of respiratory health in early childhood



- Vitamin D supplementation prevents acute respiratory infections in those who are vitamin D deficient
- In an ethnically diverse sample NZ sample vitamin D supplementation during pregnancy and infancy reduces:
 - The proportion of children making primary care acute respiratory infection visits up to age 18 months
 - The proportion of children with house dust mite sensitization and the intensity of sensitization
 - The proportion of children making acute primary care visits described by the doctor as being for asthma
- In children with asthma vitamin D supplementation prevents asthma exacerbations

To go over again



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Understand why vitamin D status is poorer in New Zealand than in many other developed countries

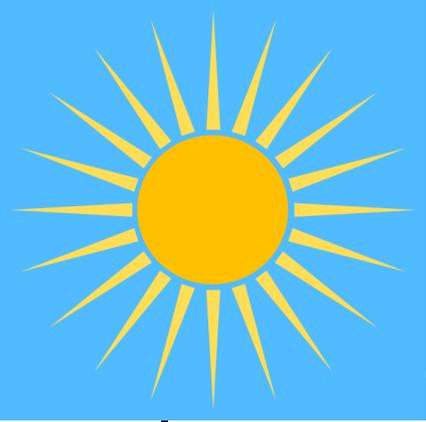


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The potential for vitamin D status to be a determinant of respiratory health in early childhood



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Vitamin D, does it help our children?



- Vitamin D is a simple and cheap intervention which prevents acute respiratory infections and possibly also asthma.
- Because vitamin D deficiency is more prevalent in Pacific and Māori vitamin D supplementation is more likely to result in improvements in their respiratory health
- Thus vitamin D supplementation is uniquely positioned to enable current ethnic disparities in respiratory health to be decreased