Vitamin D, does it help our children?

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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
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
Alfalfa

Shiitake mushrooms

Portabella mushrooms
Vitamin D dietary sources in the USA

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

<table>
<thead>
<tr>
<th>Mandatory fortification</th>
<th>Fortification encouraged</th>
<th>Minimal or no fortification*</th>
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<tr>
<td>e.g. USA</td>
<td>e.g. New Zealand</td>
<td>e.g. Australia</td>
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The amount we think you need

Includes Japan & Norway

Calvo MS et al. J Nutr 2005;135:310-6
Vitamin D deficiency is prevalent in young New Zealand children

Newborns in New Zealand (Christchurch and Wellington)

- Vitamin D deficiency*: 43%
- Severe vitamin D deficiency**: 38%
- Normal vitamin D: 19%

6 to 23 month olds in NZ (Auckland)

- Vitamin D deficiency*: 36%
- Severe vitamin D deficiency**: 55%
- Normal vitamin D: 9%

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.

It's 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

Average serum 25 OH vitamin D nmol/L

Age group

Women of childbearing age

Infants

School aged children

Lower limit of normal

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
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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 India\(^6\)

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.

**Innate**
- Epithelium
- Cathelicidin & β2-defensin
- Macrophage

**Vitamin D**
- Dendritic cell maturity

**Adaptive**
- T cells
- B cells
- Immunomodulatory cytokines
- Pro-inflammatory cytokines

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

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

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.
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 ≥ 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:

- **Enrolment & randomisation at 27 weeks gestation**
  - Mother from 27 weeks gestation until child is born:
    - Vitamin D$_3$ 2000 IU/day
    - Vitamin D$_3$ 1000 IU/day
    - Placebo
  - Infant from birth to age 6 months:
    - Vitamin D$_3$ 800 IU/day
    - Vitamin D$_3$ 400 IU/day
    - Placebo

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

- Placebo: 98%
- Lower dose vitamin D: 95%
- Higher dose vitamin D: 86%

Higher dose vs. placebo: \( p = 0.007 \)
Lower dose vs. placebo: \( p = 0.40 \)

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

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**
  - Vitamin D$_3$ 2000 IU/day
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  - Placebo

- **Infant from birth to age 6 months**
  - Vitamin D$_3$ 800 IU/day
  - Vitamin D$_3$ 400 IU/day
  - Placebo

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.

- **House dust mite**
  - Placebo: 9
  - Lower dose vitamin D: 3
  - Higher dose vitamin D: 3

- **Cat**
  - Placebo: 2
  - Lower dose vitamin D: 3
  - Higher dose vitamin D: 3

- **Grass pollen**
  - Placebo: 0
  - Lower dose vitamin D: 0
  - Higher dose vitamin D: 0

Statistical significance:
- Lower dose versus placebo: $P = 0.28$
- Higher dose versus placebo: $P = 0.03$
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**

### Number of Individuals

<table>
<thead>
<tr>
<th>Mite aeroallergens</th>
<th>Mother placebo/Infant placebo</th>
<th>Mother 1000IU/Infant 400IU D₃/day</th>
<th>Mother 2000IU/Infant 800IU Vit D₃/day</th>
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### 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

- **Cold:** Placebo 0.90, Lower dose vitamin D 0.80, Higher dose vitamin D 0.41
- **Otitis media:** Placebo 0.49, Lower dose vitamin D 0.43, Higher dose vitamin D 0.002
- **URI:** Placebo 0.82, Lower dose vitamin D 0.76, Higher dose vitamin D 0.64

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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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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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.