

Pneumococcus, Rotavirus, Varicella Vaccines — what's new?

Rotorua GP CME North, 11th June 2011

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Agenda

8.30	Introduction
8.35	Pneumococcal disease & <i>Synflorix</i>
9.15	Rotavirus
9.55	Varicella
10.20	Questions and discussion



Objectives

- Describe the epidemiology of pneumococcal disease in New Zealand
- Understand the design of *Synflorix*[®]
Pneumococcal polysaccharide conjugate vaccine, 10-valent adsorbed
- Explain practicalities of schedule change for pneumococcal vaccination
- Describe rotavirus gastroenteritis and varicella infection in NZ and globally
- Describe the available vaccines for rotavirus and varicella
- Suggested approaches of rotavirus and varicella vaccines in general practice



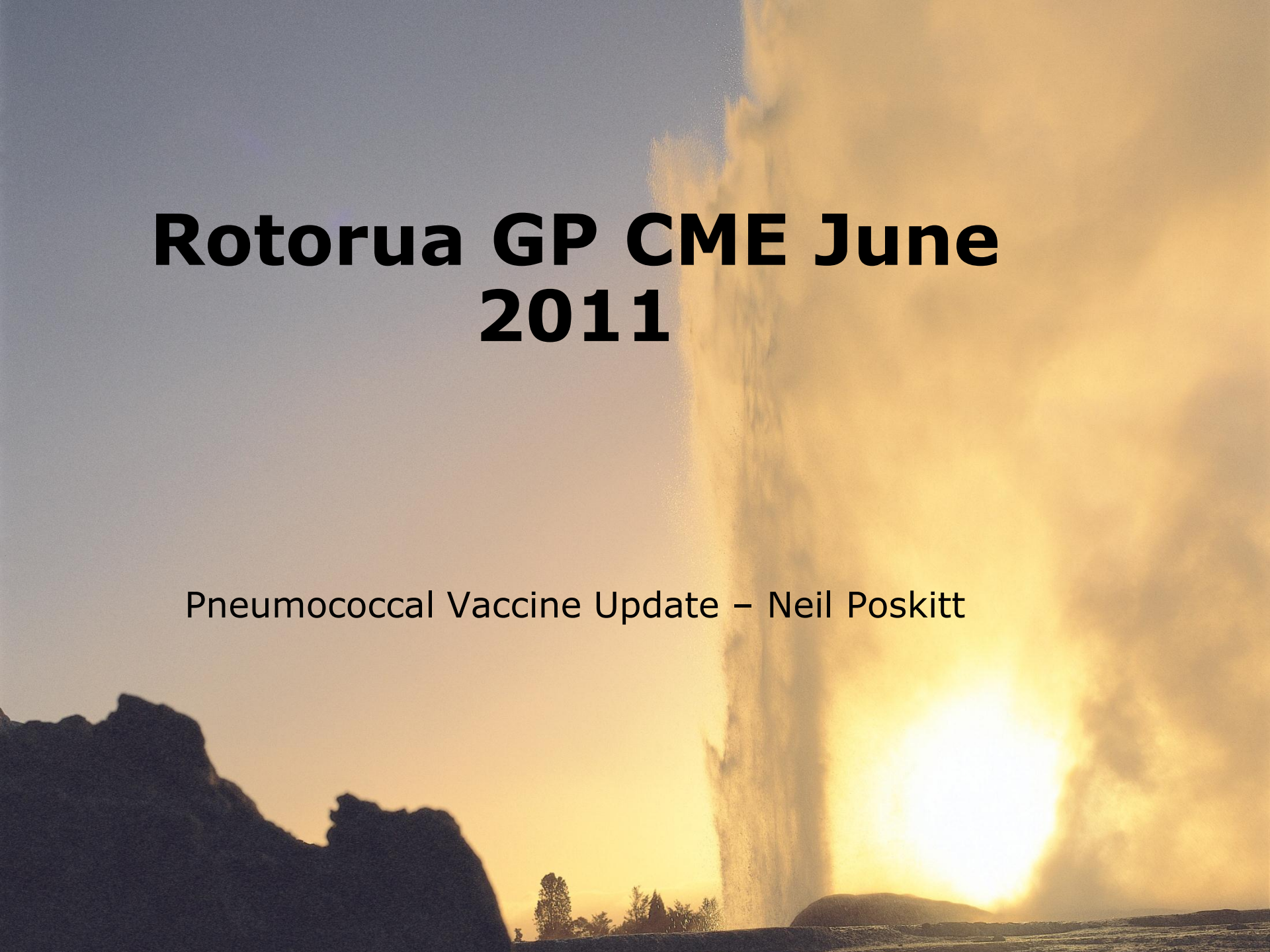
Housekeeping

- Please switch your mobile phones to silent
- This is an interactive forum, where audience discussion is encouraged



Rotorua GP CME June 2011

Pneumococcal Vaccine Update – Neil Poskitt







Synflorix®

The next-generation of pneumococcal vaccination in New Zealand



Pneumococcal polysaccharide conjugate vaccine,
10-valent adsorbed

Topics covered

- ***Streptococcus pneumoniae* – burden of disease, serotypes**
- **Impact of *Prevenar*® (Pneumococcal conjugate vaccine, 7-valent)**
- **Changes of serotypes over time**
- **Design of *Synflorix***
- **Additional protection provided**
- **Safety and tolerability**
- **Practical implementation issues**

Acknowledgements

🌿 **GSK**

🌿 **Rotorua Paediatricians**

🌿 **Graeme Simpson**

Quiz

1. Who is this?

2. What does he have to do with immunisation?



Quiz

3. Name 2 invasive diseases caused by *Streptococcus pneumoniae*
4. Name 2 complications of pneumococcal meningitis





Quiz

6. What groups of people are at increased risk from invasive pneumococcal disease?

7. What impact has PCV7 had on Invasive Pneumococcal Disease in NZ?

Quiz

8. Have pneumococcal serotypes changed in NZ since PCV7 was introduced?

9. Why do we use conjugated vaccines for children?



Quiz

11. What are the 2 main bacterial causes of otitis media?



1. Who is this?

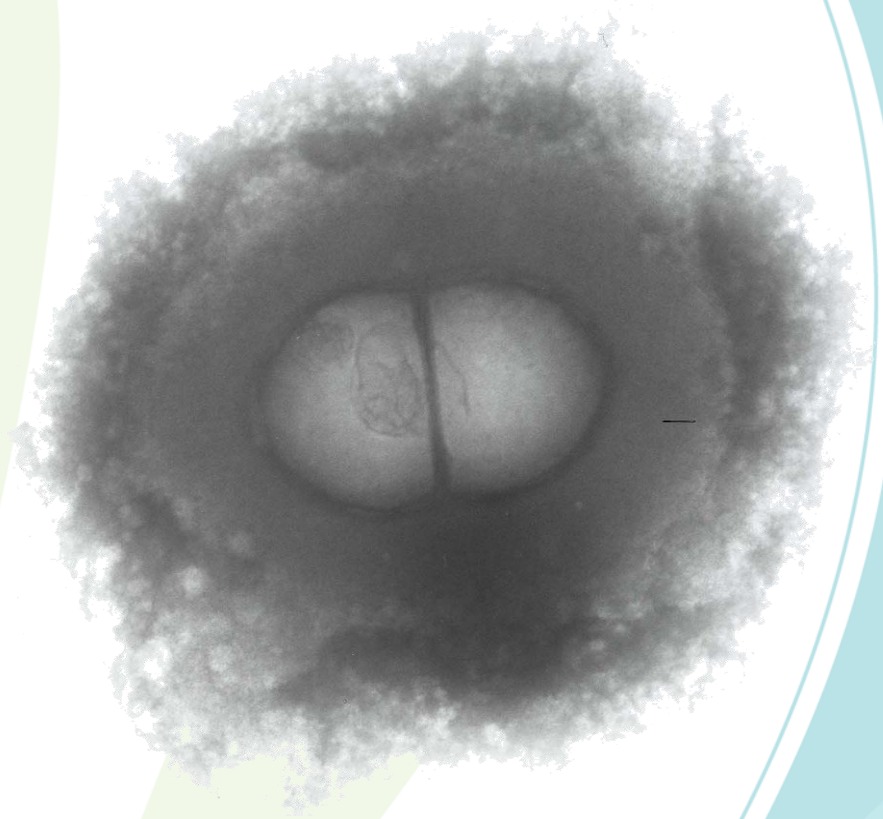
2. What does he have to do with immunisation?



Pneumococcal disease and rationale for vaccine design

Pneumococcal disease is caused by *Streptococcus pneumoniae*

- *S. pneumoniae* is a gram-positive diplococcus with a polysaccharide capsule^{1,2}
- >90 serotypes with different polysaccharide chains^{1,2}
- Normal inhabitant of human nasopharynx²
- Use of antibiotics has caused resistant strains to emerge¹⁻³

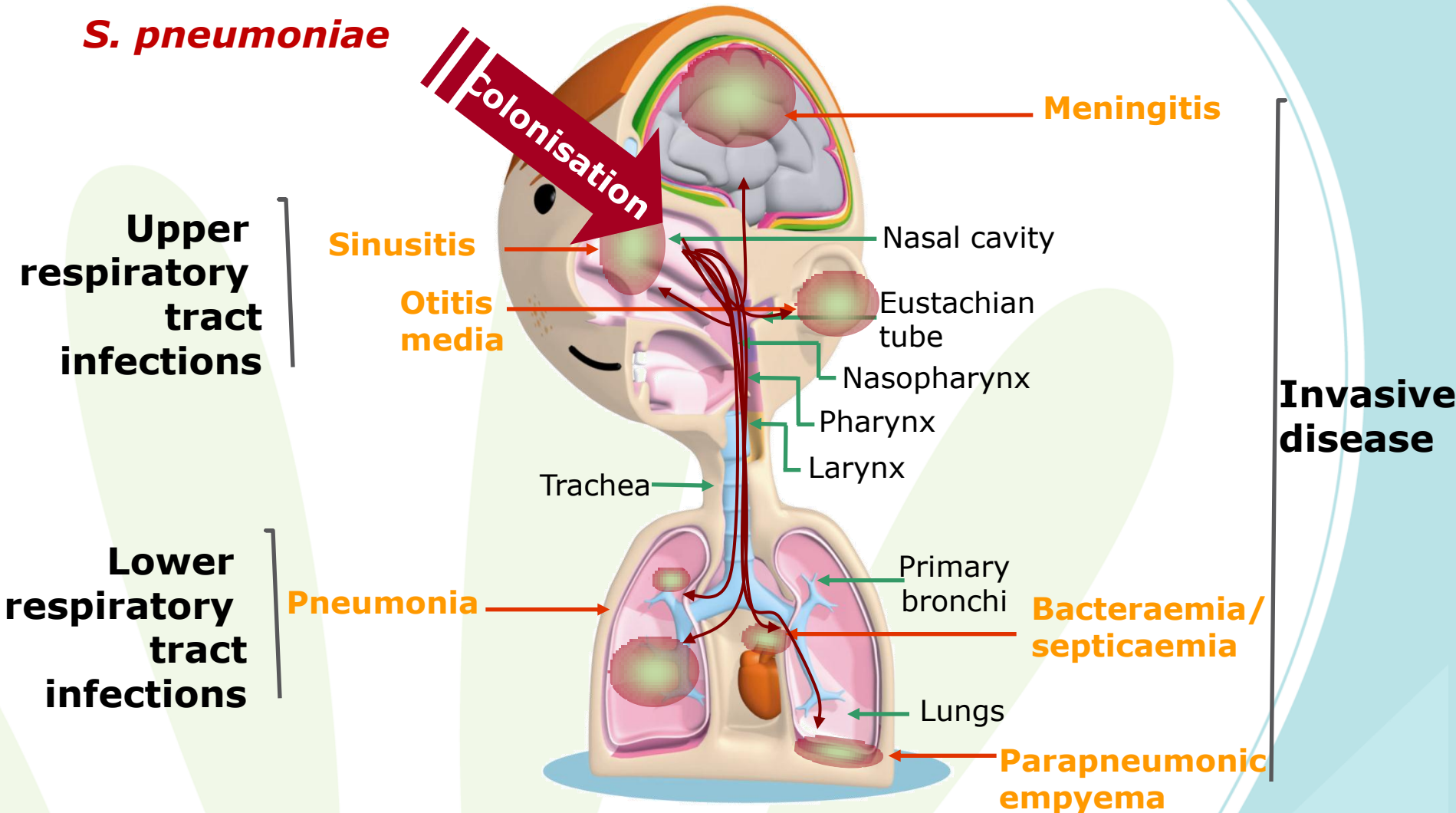


Questions 3 and 4

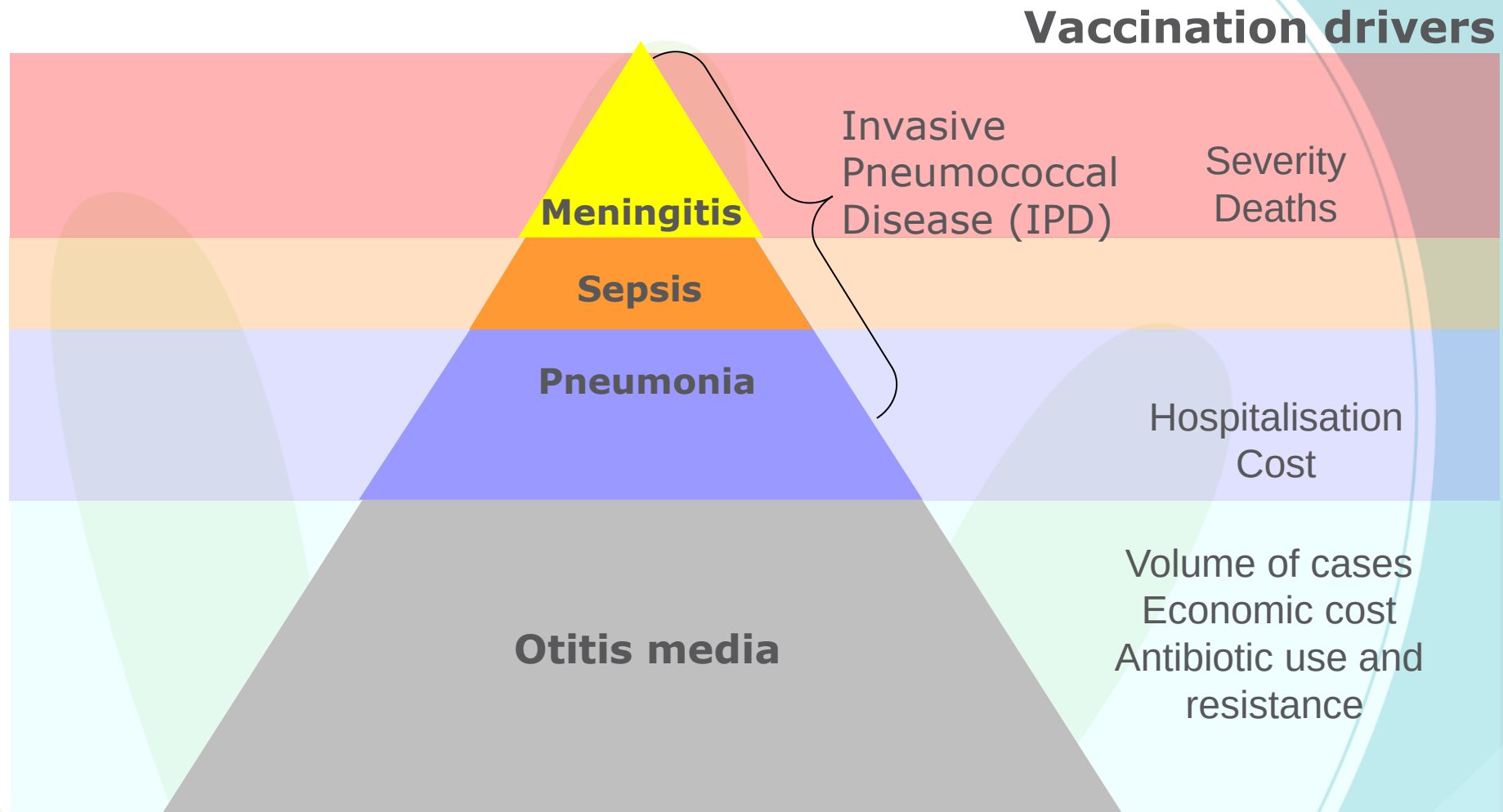
- 3. Name 2 invasive diseases caused by *S pneumoniae*?**
- 4. Name 2 complications of pneumococcal meningitis**

Pneumococcal bacteria cause disease when they spread beyond the nasopharynx

S. pneumoniae



***Streptococcus pneumoniae* causes a spectrum of invasive and non-invasive disease**



Invasive Pneumococcal Disease in New Zealand children

- ✿ <2yr – annual rate of IPD 100/100,000 during 1998 – 2005**
- ✿ <2yr – pneumococcal meningitis 2005 to 2007 annual rate 17/100,000**
- ✿ 10% die**
- ✿ 18% survivors have persistent neurological disability**



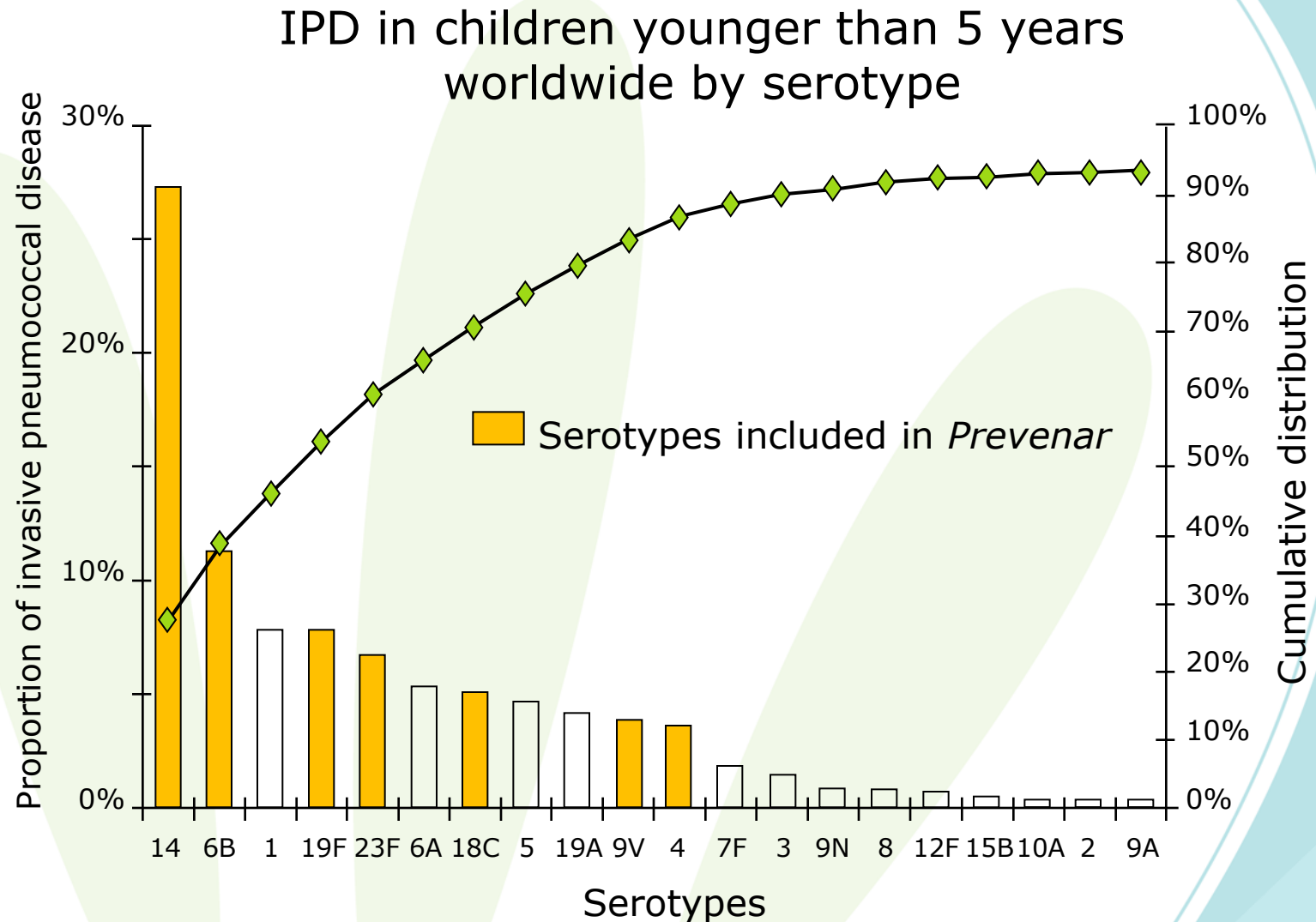
Question 6

What groups of people are at increased risk from invasive pneumococcal disease?

Risk of Invasive Pneumococcal Disease

- ✿ **Much higher in infants and elderly**
- ✿ **Predisposing conditions – viral URTI**
- ✿ **Underlying conditions/medications affecting immune function e.g. asplenia**
- ✿ **Higher rates in Maori and PI children**

Serotypes that cause invasive pneumococcal disease worldwide

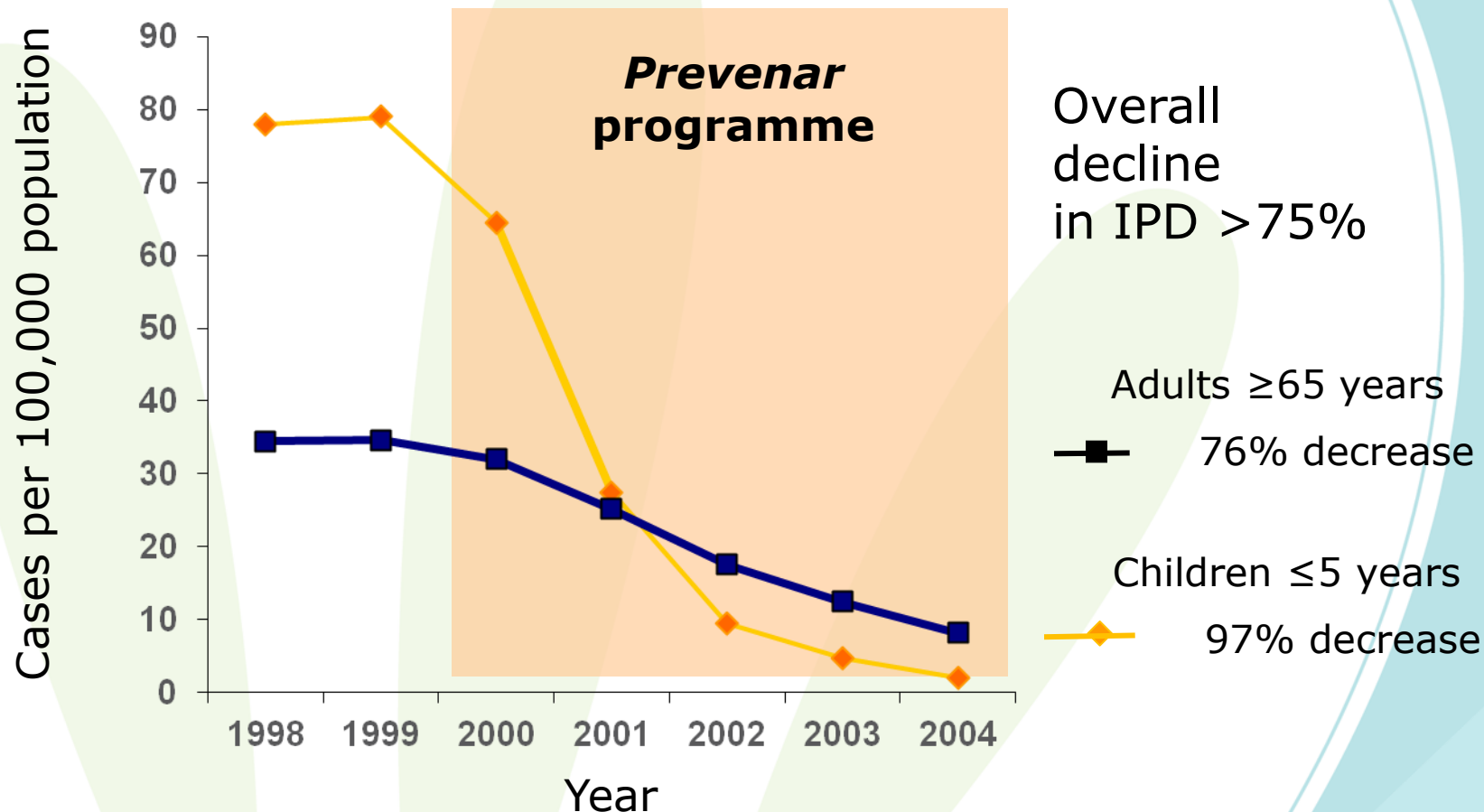


Impact of PCV7 (*Prevenar*)

Pneumococcal Conjugate Vaccine, 7-valent

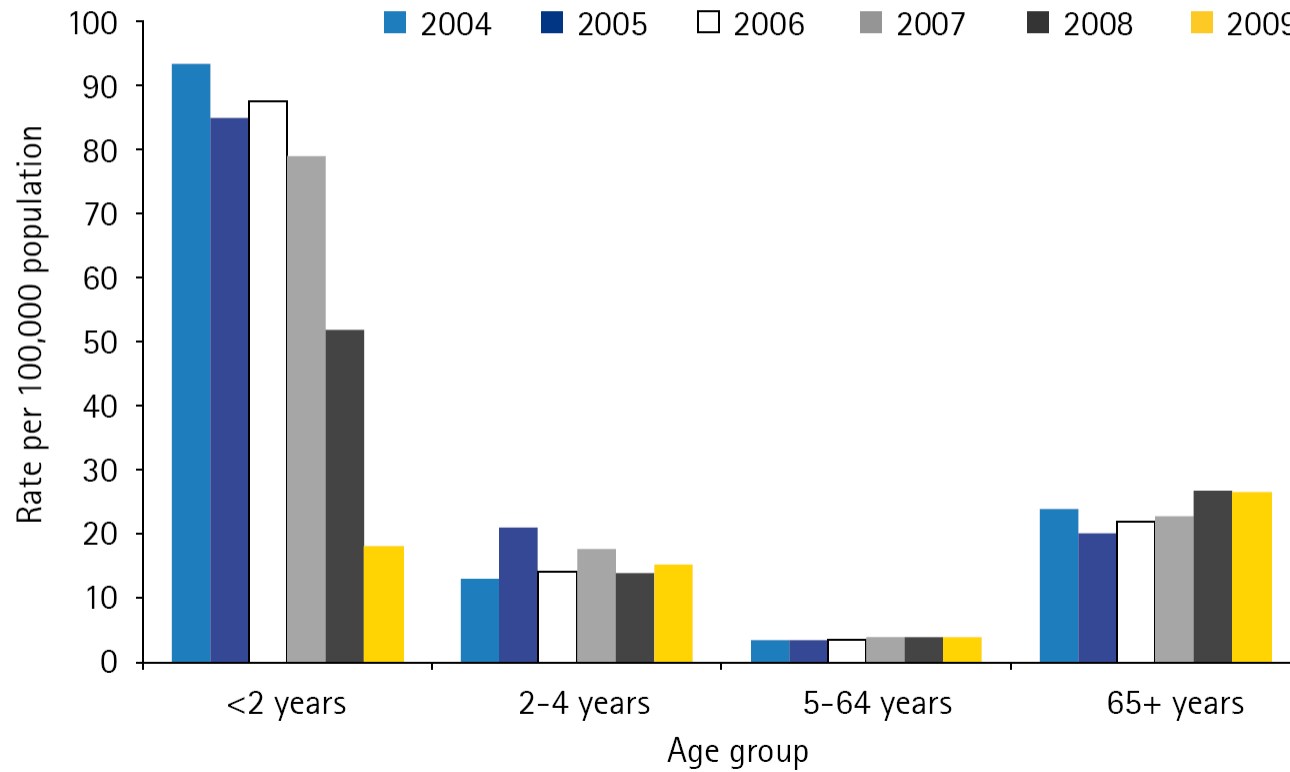
***Prevenar* immunisation programmes in the USA have reduced IPD and caused herd protection**

Rate of invasive pneumococcal disease caused by *Prevenar* serotypes in the USA



***Prevenar* immunisation in New Zealand has also reduced IPD**

Figure 2. Rates of invasive pneumococcal disease caused by PCV-7 serotypes, by age group each year 2004–2009



Question 8

Have pneumococcal serotypes changed in NZ since PCV was introduced?

Serotypes that cause invasive pneumococcal disease can vary over time

- ✿ Serotype 1 has risen in NZ in recent years¹ and is one of the most prevalent serotypes in IPD globally²
- ✿ In 2009 in NZ, serotype 1
 - was the most prevalent cause of IPD in the total population¹
 - was the most prevalent cause of IPD in children younger than 2 years¹
 - was the second most prevalent serotype after serotype 14 in children under 5 years of age¹
- ✿ The incidence of 19A has been steady in NZ over recent years, with no increase observed since the introduction of *Prevenar*^{1,3,4}

Serotypes not covered by *Prevenar*

- ✿ **Serotypes 1, 5, and 7F together account for about 15% of global pneumococcal morbidity and mortality.¹**
- ✿ **The WHO requires that future pneumococcal vaccines contain serotypes 1 and 5, since they cause a large proportion of severe disease.²**
- ✿ **In NZ in 2009 serotypes 1, 5 and 7F accounted for 17% of IPD in children aged <5 years.³**

Question 9

Why do we use conjugated vaccines for young children?

Design of *Synflorix*

Composition of *Synflorix* – designed as a dual-pathogen vaccine

S. pneumoniae

Non-typeable
H. influenzae

Polysaccharides

**Main carrier protein:
Protein D**

TT DT
4, 6B, 9V, 14, 18C, 19F, 23F

1, 5, 7F

NTHi Protein D

- 8 serotypes conjugated to protein D
- 18C conjugated to tetanus toxoid (TT)
- 19F conjugated to diphtheria toxoid (DT)

Synflorix is indicated for the active immunisation of infants and children from the age of 6 weeks up to 5 years against disease caused by *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F (including invasive disease, pneumonia and acute otitis media)

Vaccine profiles and cross-reactive responses

	Main carrier protein*	<i>S. pneumoniae</i> serotypes			
<i>Prevenar</i>	CRM197	4, 6B, 9V, 14, 18C, 19F, 23F			6A
<i>Synflorix</i>	NTHi protein D	4, 6B, 9V, 14, 18C, 19F, 23F	TT	DT	1, 5, 7F
					6A
					19A

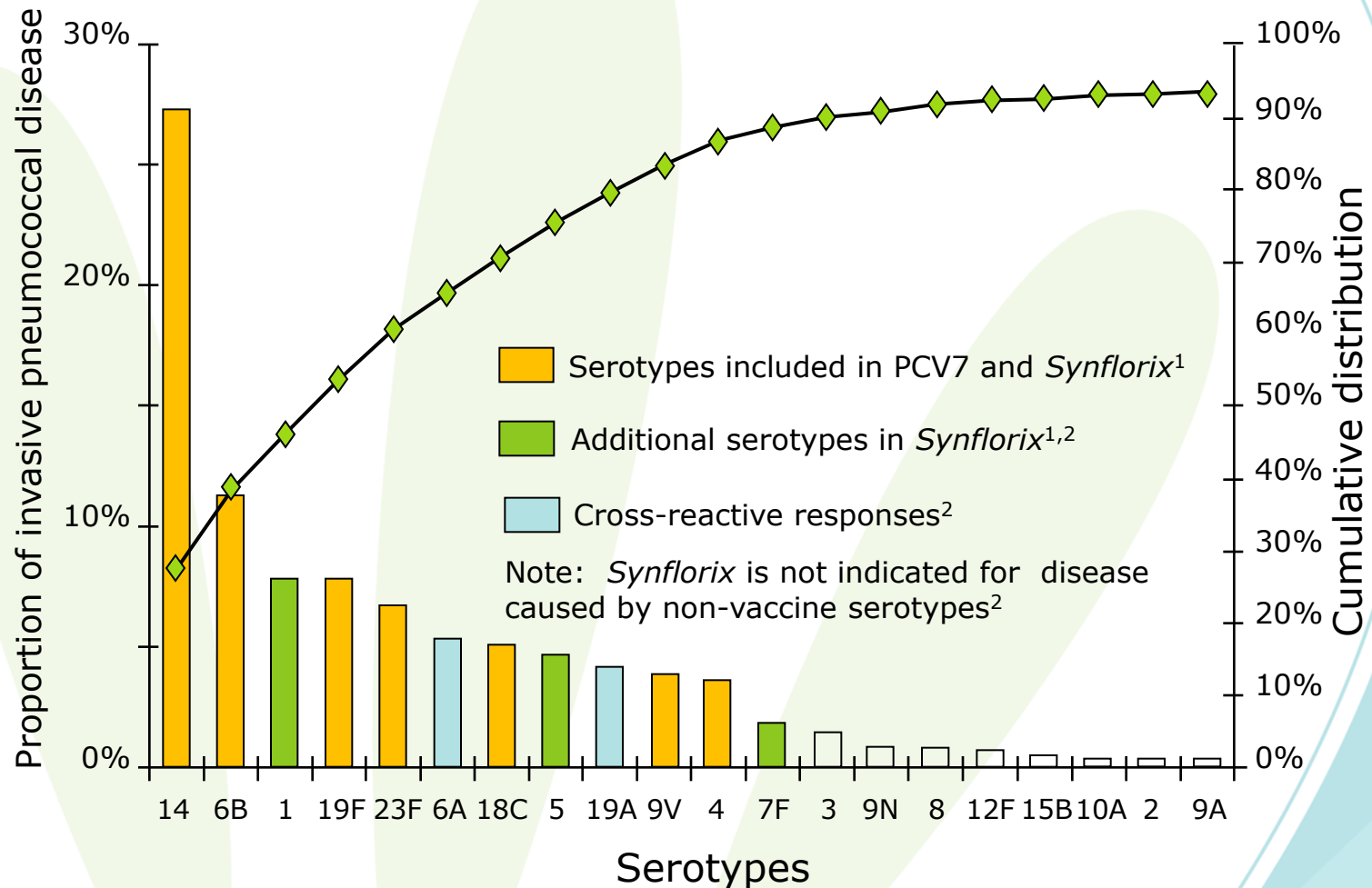
*In *Synflorix*, 18C is conjugated to tetanus toxoid and 19F to diphtheria toxoid.¹

Synflorix induces functional antibodies to 6A and 19A.¹

Note: Data on cross-reactive immune responses are reviewed in the *Synflorix* Data Sheet.¹
Synflorix is not indicated for serotypes other than those included in the vaccine.¹

***Synflorix* increases coverage of IPD worldwide**

IPD in children younger than 5 years worldwide by serotype



Summary: the design of *Synflorix*

- ✿ *Synflorix* extends protection against pneumococcal disease through inclusion of serotypes 1, 5, and 7F.¹

Additional design features:

- ✿ Inclusion of 6B and 19F stimulates cross-reactive functional immune responses to pneumococcal serotypes 6A and 19A.^{1,2}
- ✿ Inclusion of Protein D enables immune responses against not only *S. pneumoniae* but also NTHi¹⁻⁵

Note: Data on immune responses to cross-reactive serotypes and NTHi are reviewed in the *Synflorix* Data Sheet.¹ *Synflorix* is only indicated against disease caused by vaccine serotypes.¹ Large-scale effectiveness studies are ongoing.^{6,7}

¹GSK NZ. *Synflorix*® Data Sheet. 2010. ²Wysocki et al. *Pediatr Infect Dis J* 2009;28:S77–88. ³Hausdorff et al. *BMC Pediatr* 2010;10:4.

⁴Prymula et al. *Lancet* 2006;367:740–748. ⁵Schuerman. *Vaccine* 2009;27:5748-5754. ⁶GSK. COMPAS (Clinical Otitis Media & Pneumonia Study). 2007. ⁷GSK. Pneumococcal Conjugate Vaccine 1024850A (FinIP). 2009.



Question 11

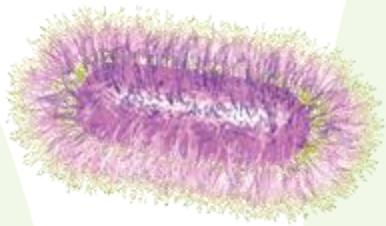
What are the 2 main bacterial causes of otitis media?

The need for protection against acute otitis media in NZ

Classification of *H. influenzae*

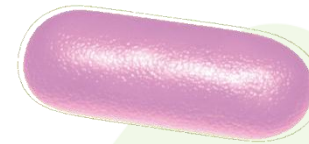
- *H. influenzae* is a gram-negative coccobacillus with two main forms:¹

H. influenzae



Six serotypes with different capsular polysaccharides (a–f) classified by reactions with antisera

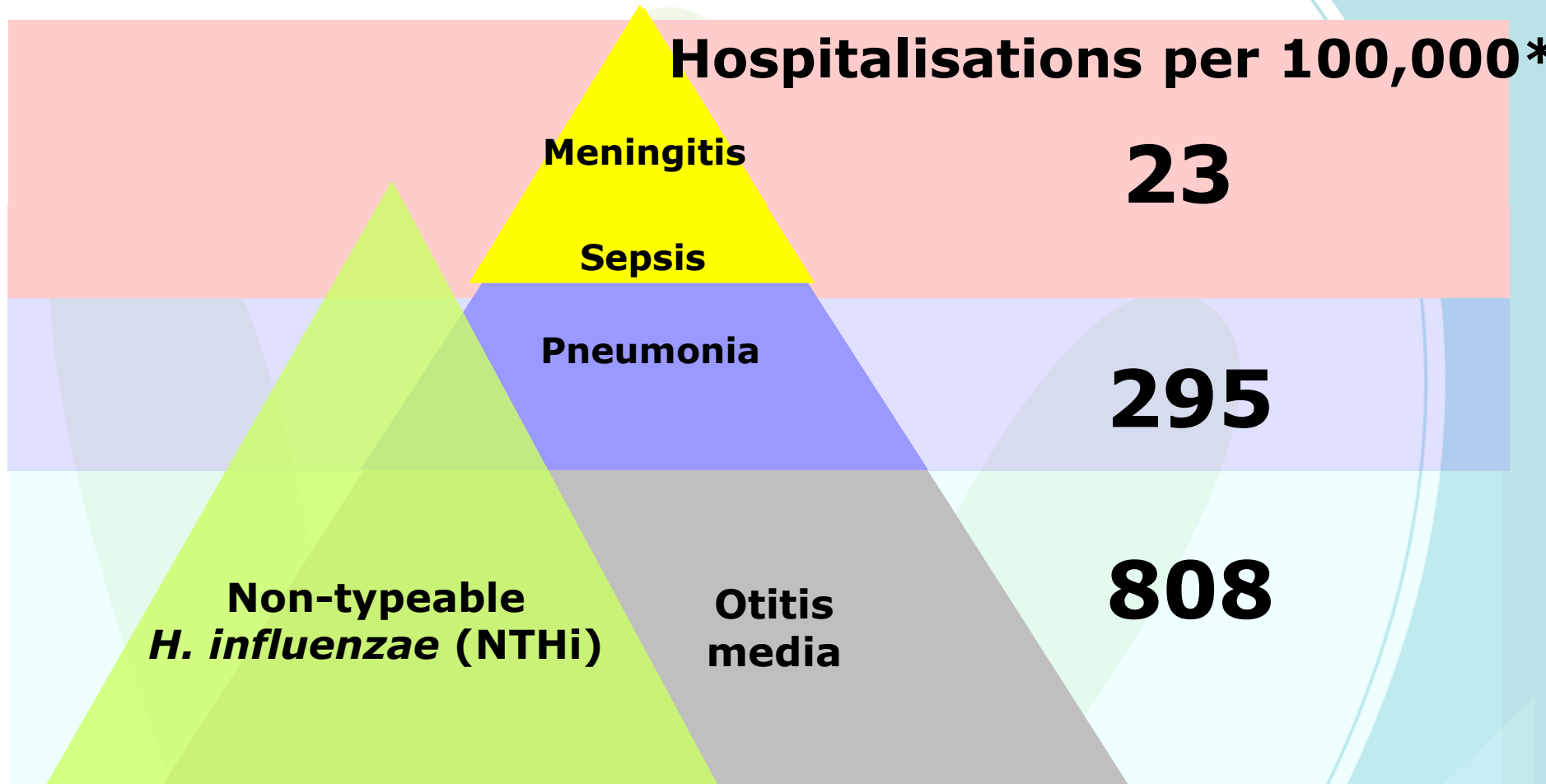
Non-typeable *H. influenzae*



Does not react with *H. influenzae* polysaccharide antisera and hence non-typeable

- The *H. influenzae* type b (Hib) vaccine does not protect against disease caused by NTHi because it is specific for type b polysaccharide capsule.¹

***S. pneumoniae* and NTHi cause an overlapping spectrum of disease**



*Hospitalisations in children younger than 5 years before implementation of PCV7 immunisation in NZ.

Ear infections are a significant burden on the NZ healthcare system

- ✿ Every year, NZ children under 5 years of age account for:
 - 83,000 GP consultations for new cases of otitis media¹
 - 5,000 hospital admissions for otitis media²
 - Antibiotics are prescribed for at least 50% of cases presenting to GPs¹

- ✿ Ethnic disparities in ear health:
 - Hospital admissions for Maori and Pacific Island children with acute otitis media are twice those for other children^{3,4}

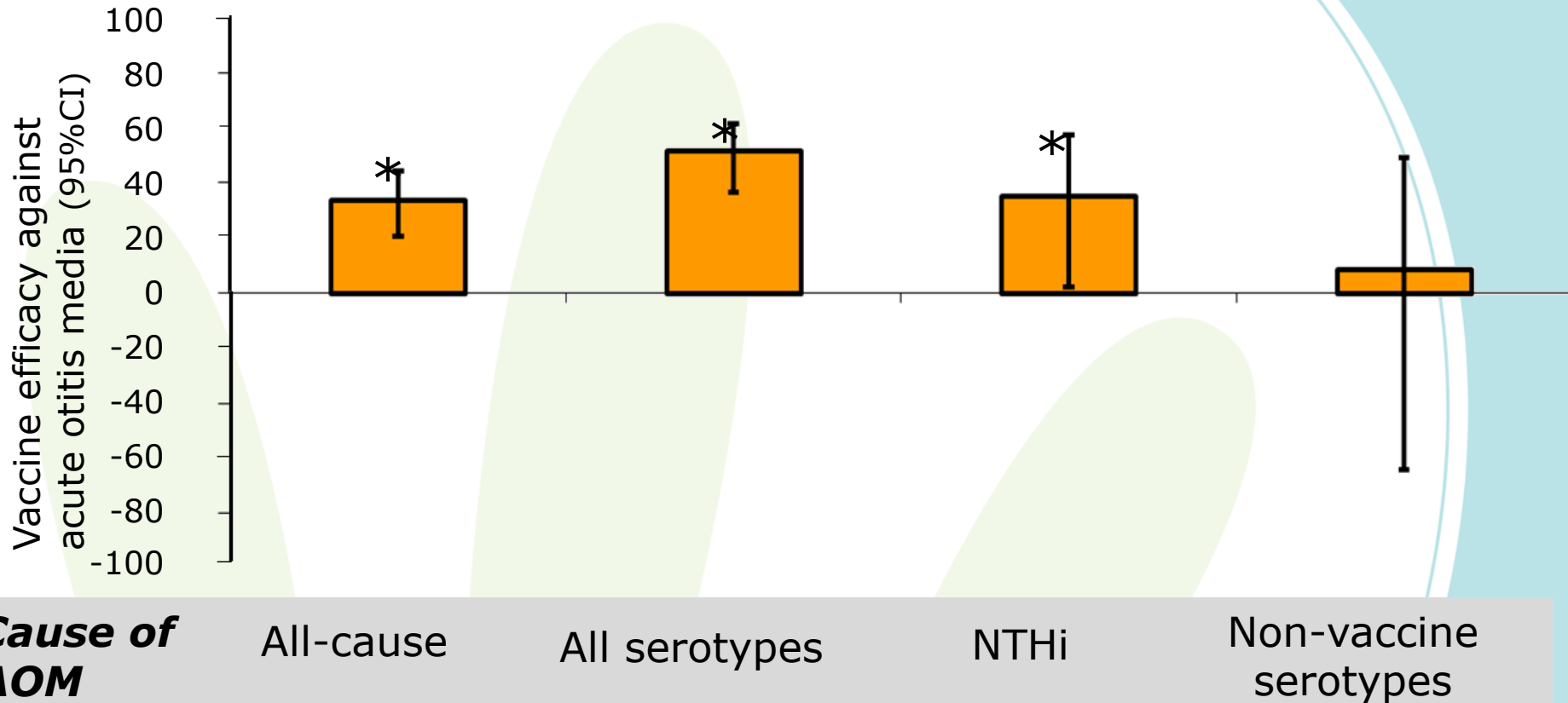
Ear infections can affect hearing, and can delay learning

- ✿ If left untreated, otitis media can affect hearing¹
 - Hearing impairment in young children can impede learning, speech, and cognitive abilities, with associated reduction of quality of life.^{2,3}
- ✿ Ethnic disparities in ear health:
 - New entrant hearing check failure rates in NZ 11% PI, 10% Maori and 4% in European children.

Pneumococcal Otitis Efficacy Trial (POET) study design

- ❖ **Double blind**, randomised (1:1) study in Czech and Slovak Republics
- ❖ **Control:** hepatitis A vaccine (*Havrix*®)
- ❖ **11-valent *Synflorix* prototype**
 - 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F (1 µg each)
 - All serotypes conjugated to protein D from *H. influenzae*
- ❖ **Schedule:** 3 doses (at 3, 4, and 5 months) + booster (at 12–15 months)
- ❖ **Study population:** ~5000 infants, with 24-month follow-up
- ❖ **Coadministration:** DTaP-IPV-HepB-/Hib vaccine (*Infanrix-hexa*®)

A prototype for *Synflorix* was effective against AOM caused by *S. pneumoniae* and NTHi



*Statistically significant effect

Note: Data on protection against otitis media are reviewed in the *Synflorix* Data Sheet;² *Synflorix* is not indicated for immunisation against disease caused by NTHi.²

Summary - Synflorix

- ✿ *Synflorix* is a pneumococcal conjugate vaccine containing 10 serotypes of *S. pneumoniae*¹
- ✿ Contains the same 7 serotypes as *Prevenar* with the addition of serotypes 1, 5 and 7F thereby extending the cover against IPD, pneumonia and OM²
- ✿ It also stimulates immune responses to NTHi – an important pathogen in acute otitis media.^{1,3}

Vaccine implementation

Synflorix is generally well-tolerated

- ✿ Combined analysis of clinical studies of safety in more than 4,000 healthy infants:¹
 - The most common adverse reactions observed after primary vaccination were pain, redness, and swelling at the injection site, irritability, fever, and drowsiness.¹
 - Most reactions were of mild to moderate severity and were not long-lasting.¹
 - No safety concerns were identified.¹
- ✿ The safety and tolerability profile of *Synflorix* is similar to that of *Prevenar* and commonly coadministered vaccines.¹
 - Fever >38°C within same range as PCV7 post-primary and booster.
 - Fever >40°C was infrequent: ≤1% of *Synflorix* doses and ≤2% of PCV7 doses.¹

¹Chevallier et al. *Pediatr Infect Dis J* 2009;28:S109–118.

Global use of *Synflorix* (April 2011)

- First registered in December 2008
- Now approved in 83 countries

National
immunisation
programmes:

2 + 1 schedule

- Colombia (Bogotá)
- Finland
- Mexico
- Sweden (3 provinces)

3 + 0 schedule

- Kenya

3 + 1 schedule

- Australia (Northern Territory)
- Austria (high-risk groups)
- Albania
- Brazil
- Bulgaria
- Cyprus
- Hong Kong
- Taiwan (Taipei)
- The Netherlands (high-risk groups)

From July 2011, *Synflorix* will replace *Prevenar* on the NZ Immunisation Schedule

New Zealand National Immunisation Schedule from 1 September 2008

Age	DTaP-IPV-HepB/Hib IM	PCV7 ² IM	Hib IM	MMR SC	DTaP-IPV IM	dTap IM	HPV IM	Td IM	Influenza IM
6 weeks	Infanrix® - hexa	<i>Synflorix</i> ®							
3 months	Infanrix® - hexa	<i>Synflorix</i> ®							
5 months	Infanrix® - hexa	<i>Synflorix</i> ®							
15 months		<i>Synflorix</i> ®	Hiberix™	MMR® II					
4 years				MMR® II	Infanrix™-IPV				
11 years						Boostrix®			
12 years ¹ (School year 8) Starts in 2009							Gardasil® ³		
							Gardasil® ³ 2 months after 1 st dose		
							Gardasil® ³ 4 months after 2 nd dose		
45 years ⁴								ADT®-Booster ⁵	
65 years ⁵								ADT®-Booster ⁵	Influenza (annually) ⁵

1. Gardasil® (HPV) catch-up programme:

- from 01 Sept 2008 for girls born in 1990 & 1991.
- phased from 2009 & 2010 for girls born after 01 Jan 1990 & aged 12-18 years.
- For details of the programme see MoH website or information from your DHB.

2. *Prevenar*® (PCV7) is free for infants born from 01 January 2008. 3. *Prevenar*® (PCV7) fourth dose, given at 15 months of age, starts April 2009 for infants born from 01 Jan 2008. 4. ADT®-Booster vaccine is free for 45 & 65 year olds. There is no immunisation claim payable to the administrator. 5. Influenza vaccination for adults and children from 6 months old with certain chronic medical conditions – see Immunisation Handbook (Ministry of Health).

Additional vaccines for special groups

Birth: BCG vaccine for babies at high risk from tuberculosis (TB)
– see Immunisation Handbook (Ministry of Health).
Hepatitis B vaccine plus hepatitis B immunoglobulin for infants of hepatitis B carrier mothers.

Children < 5 years at high risk of invasive pneumococcal disease:
Pneumococcal vaccination (conjugate or polysaccharide) – see 2008 National Immunisation Schedule Health Provider Booklet (Ministry of Health).

Children and adults with splenectomy and/or functional asplenia:
Pneumococcal, Hib, MenZB™ and Meningococcal A, C, Y, W-135 vaccines – see 2008 National Immunisation Schedule Health Providers Booklet (Ministry of Health).

Hepatitis B carriers:
Immunisation for household and sexual contacts.

Women:
MMR vaccine for women of childbearing age who are susceptible to rubella.

Vaccine key: BCG: tuberculosis; DTaP: diphtheria, tetanus, acellular pertussis - child; dTap: diphtheria, tetanus, acellular pertussis - adolescent/adult; HepB: hepatitis B; Hib: *haemophilus influenzae* type b; HPV: human papilloma virus; IPV: inactivated polio vaccine; MenZB: meningococcal b; MMR: measles, mumps, rubella; PCV7: pneumococcal; Td: tetanus, diphtheria – adult.

Immunisation Advisory Centre PO Box 17 360, Greenlane, Auckland. Telephone: (09) 373 7599 ext 86191 E-mail: imac@auckland.ac.nz

For detailed vaccine prescribing information please refer to the data sheet via the Medsafe website www.medsafe.govt.nz or the Immunisation Handbook (Ministry of Health) www.moh.govt.nz or phone 0800 IMMUNE (466863)



0800 IMMUNE
4 6 6 8 6 3

www.immune.org.nz

Synflorix can be coadministered with other vaccines available in NZ

- ❖ Vaccines on the Immunisation Schedule:¹
 - DTaP-IPV-HepB-/Hib²⁻⁶ (*Infanrix-hexa*, *Infanrix-IPV*)
 - MMR⁷

- ❖ Approved but not funded on the NZ Immunisation Schedule:¹
 - Hib MenC^{2,6}
 - Rotavirus vaccine⁸ (e.g. *Rotarix*)
 - Varicella vaccine⁷ (e.g. *Varilrix*)

- ❖ Before prescribing *Synflorix*, please review the full Data Sheet¹ at www.medsafe.govt.nz

The transition from *Prevenar* to *Synflorix*

- Existing stocks of *Prevenar* will be used up first and then all children will be switched to *Synflorix* – Aug/Sept 2011
- Children who have received one or more doses of *Prevenar* can be switched to *Synflorix* at any point in their schedule to complete their pneumococcal vaccine course.²
- The number and timing of doses of *Prevenar* and *Synflorix* are the same
 - Children will still receive their pneumococcal vaccines at 6 weeks, 3, 5 and 15 months of age

1. Ministry of Health. Announcement – Changes to the National Immunisation Schedule for July 2011. Available at: <http://www.moh.govt.nz/moh.nsf/indexmh/immunisation>. Accessed 11 May 2011. 2. Ministry of Health. Update: National Immunisation Schedule changes from 1 July 2011. Available at: <http://www.moh.govt.nz/moh.nsf/indexmh/immunisation>. Accessed 11 May 2011.

Pneumococcal catch-up programme for children aged <5 years

✿ The catch-up programme for children aged <2 years will be the same as it is for *Prevenar*

Age	0–6 months	7–11 months	12–59 months
Number of doses	3 doses, given at 6 weeks, 3 and 5 months + 1 dose at 15 months	2 doses, given 6–8 weeks apart + 1 dose at 15 months	2 doses, given 8 weeks apart

Children at high risk of pneumococcal disease are those:

- ✿ On immunosuppressive therapy or radiation therapy
- ✿ With primary immune deficiencies
- ✿ With HIV infection
- ✿ With renal failure, or nephrotic syndrome
- ✿ Who are immune-suppressed following organ transplantation
- ✿ With cochlear implants or intracranial shunts
- ✿ With cerebrospinal fluid leaks
- ✿ Receiving corticosteroid therapy for more than two weeks (see Immunisation Handbook for full details)
- ✿ With chronic pulmonary disease (including asthma treated with high-dose corticosteroid therapy)
- ✿ Preterm infants, born before 28 weeks gestation
- ✿ With cardiac disease
- ✿ With cyanosis or failure
- ✿ With diabetes
- ✿ With Down syndrome
- ✿ Who are pre-or post-splenectomy, or with functional asplenia.

Pneumococcal vaccination for high-risk groups only

	High-risk		Pre- and post-splenectomy		Adults >65 years
	Children 0–5 years	Adults >16 years	Children 0–16 years	Adults >16 years	
	Funded	Recommended	Funded	Funded	Recommended
Age-appropriate dose schedule (4 doses, at 6 weeks, 3, 5, 15 months)	PCV13		PCV13		
Previously unvaccinated children 2–5 years: 2 doses, at 8 weeks apart	PCV13				
Revaccinate >2 years of age, ≥8 weeks after last PCV dose	23PPV (2 doses, 3-year interval)		23PPV (2 doses, 3-year interval if first aged <10 years, or 5-year interval)		
Revaccinate 5 years after the first vaccination and/or at age 65 years		23PPV (3 doses)		23PPV (3 doses)	23PPV (2 doses)

Packaging and storage of *Synflorix*

- ❖ Packs of 10
- ❖ No needles
- ❖ Prefilled syringes
- ❖ Store at 2–8° C
- ❖ Do not freeze
- ❖ 3-year shelf-life
- ❖ Protect from light
- ❖ Shake well before use



Administration of prefilled syringe

- ❖ Holding the syringe barrel (not the plunger) in one hand, unscrew the syringe cap by twisting anticlockwise.
- ❖ To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock.

NEEDLE

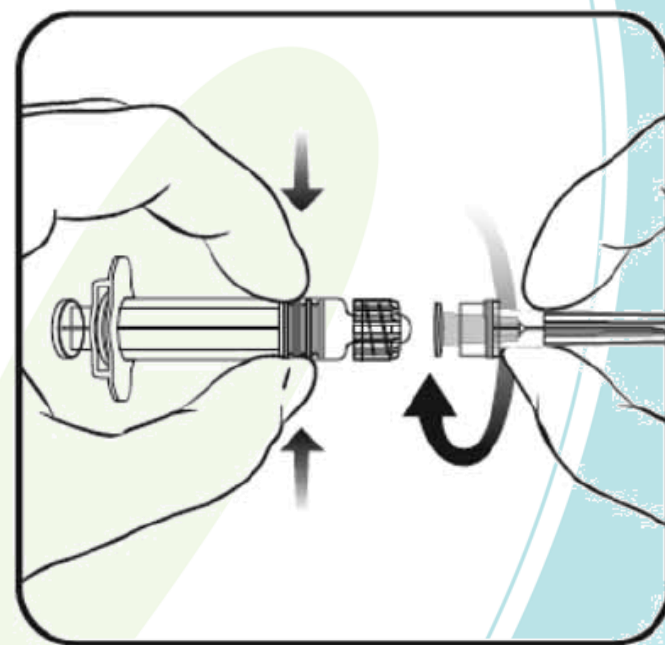
Needle protector

SYRINGE

Syringe plunger

Syringe barrel

Syringe cap

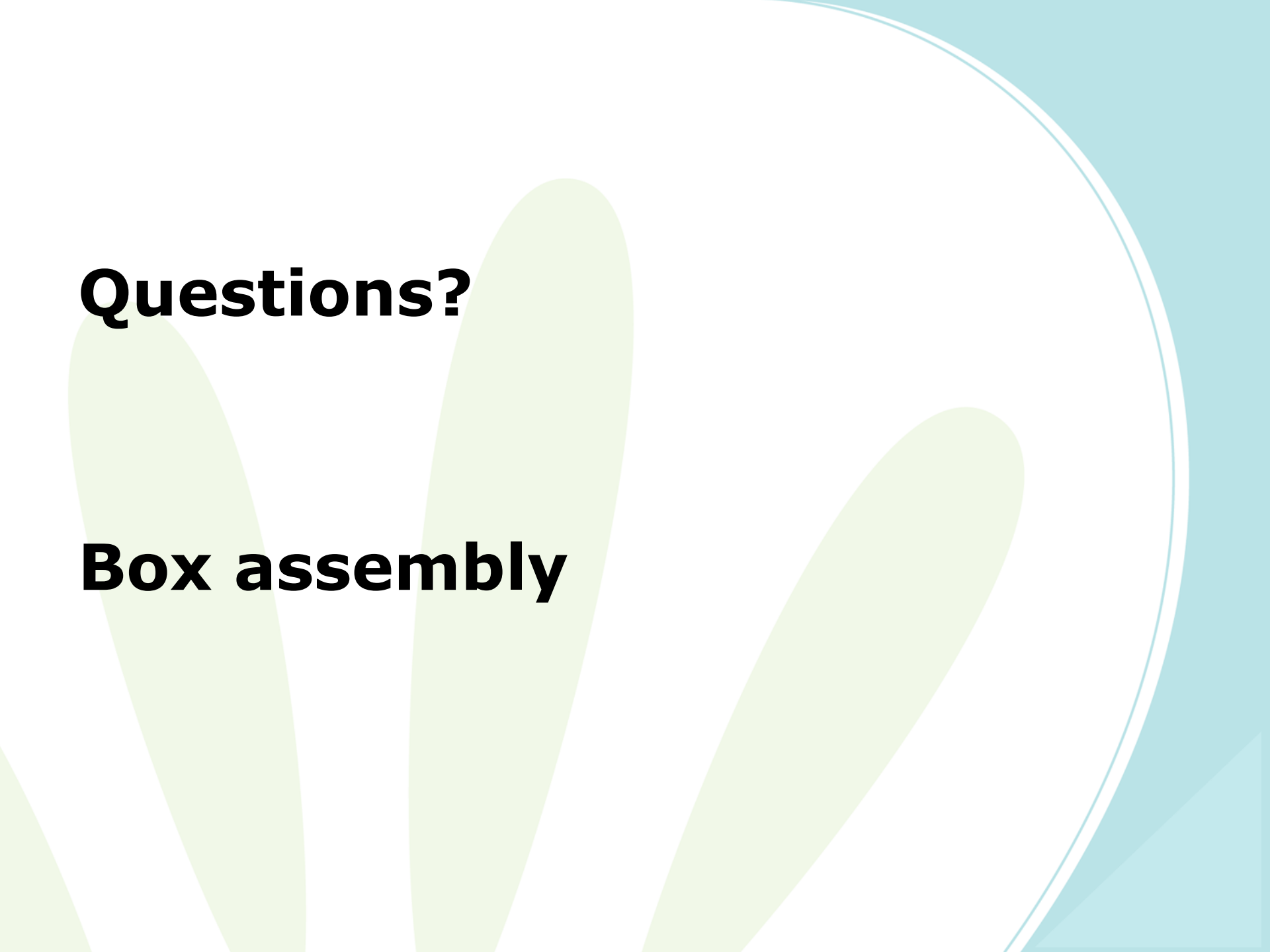


- ❖ Remove the needle protector. Administer the vaccine.

More information on *Synflorix*

- ✿ NZ Immunisation Handbook 2011
- ✿ Phone the Immunisation Advisory Centre on 0800 IMMUNE (0800 466 863)
- ✿ Go to www.immune.org.nz or www.moh.govt.nz/immunisation
- ✿ Refer to the *Synflorix* Data Sheet and Consumer Medicine Information on the Medsafe website: <http://www.medsafe.govt.nz>
- ✿ For GSK Medical Information in NZ, please call 0800 808 500 or +64 09 367 2900, and ask for the Medical Information Department.





Questions?

Box assembly

Synflorix product information

Synflorix[®] (10-valent adsorbed pneumococcal polysaccharide conjugate vaccine) is an injection for intramuscular use only. *Synflorix* is available on the National Immunisation Schedule and is a **prescription medicine** for active immunisation of infants and children from the age of 6 weeks up to 5 years against disease caused by *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F (including invasive disease, pneumonia, and acute otitis media). The recommended immunisation schedule consists of three doses beginning at 6 weeks of age, with an interval of at least 1 month between doses, plus a booster dose at least 6 months after this primary series. Each 0.5 mL dose contains 1 mcg of pneumococcal polysaccharide serotypes 1, 5, 6B, 7F, 9V, 14, and 23F and 3 mcg of pneumococcal polysaccharide serotypes 4, 18C, and 19F adsorbed onto 0.5 mg aluminium phosphate. *Synflorix* also contains approximately 13 mcg of protein D carrier protein, approximately 8 mcg of tetanus toxoid carrier protein, and approximately 5 mcg of diphtheria toxoid carrier protein. **Contraindications:** known hypersensitivity to any component of the vaccine. **Precautions:** As with all injectable vaccines, provide appropriate supervision against rare anaphylactic events. Postpone in those with acute severe febrile illness (deferral not required with minor infections, e.g. a cold). Use caution with coagulation disorders. As with all vaccines a protective immune response may not be elicited in all vaccinees. Safety and immunogenicity data not available in those with underlying medical conditions predisposing to pneumococcal infection (e.g. sickle cell disease, splenic dysfunction, HIV). Children with impaired immune response (e.g. use of immunosuppressive therapy, genetic defect, HIV infected) may have a reduced immune response to vaccination. Data suggest that the use of prophylactic paracetamol might reduce the immune response to pneumococcal vaccines; the clinical relevance of this observation remains unknown. **Common side effects:** pain, redness, swelling, and induration at injection site; fever; drowsiness; loss of appetite; and irritability. As with some other vaccines, an increase in reactogenicity was reported after booster vaccination compared to the primary course. **Interactions:** immune responses and the safety profiles of the coadministered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 vaccine, for which inconsistent results were observed across studies. No interference was observed with meningococcal conjugate vaccines irrespective of the carrier protein (CRM197 and TT conjugates). Enhancement of antibody response to diphtheria toxoid and tetanus toxoid was observed. Before prescribing *Synflorix*, please review the full Data Sheet at www.medsafe.govt.nz. *Synflorix* is a trade mark of the GlaxoSmithKline group of companies. Marketed by GlaxoSmithKline NZ Limited, Auckland. TAPS DA4311IG/11AP/150.

Rotavirus Vaccines

Rationale for Use

Stewart Reid

Conflict of interest

- GSK are paying me a stipend for preparing and giving this talk
- In the past I have received support for vaccine work, clinical trials, presentation of papers and conference attendance from NZ Ministry of Health, US Government, Fondation Merieux, International Vaccine Institute, CSL, GSK, MSD, Novartis and Pfizer.

Rotavirus vaccine should not be offered to infants because

- It's not on the schedule (and there must be a good reason for that)
- Rotavirus causes only a mild illness
- Vaccine costs too much
- Vaccine causes Intussusception and
- It is contaminated with a pig virus
- Its too difficult because it has to be given by 12 (Rotateq) or 14 (Rotarix) weeks of age

Vaccine Schedule

- Reason not included is Fiscal
- The case for including rotavirus vaccine in childhood schedule is strong
- Rotavirus vaccine has potential to improve on time coverage
- But first dose has to be given by 12 or 14 weeks (ideally 6 weeks). How do you achieve this?

ITF considerations

- Disease and Epidemiology
- Licensed product(s)
- Experience in other countries
- Fit with immunisation schedule
- Cost benefit
- Surveillance

Surveillance

- All vaccine preventable disease require comprehensive surveillance to measure success and failure of immunisation programmes
- Disease - notification and hospitalisation data
- Lab notification
- Coverage
- Adverse events

Disease and Epidemiology

Rotavirus

- Causes vomiting and diarrhoea of varying severity from relatively mild to fatal
- Most common cause of severe D&V world wide
- Treatment is supportive - rehydration
- The incidence is approximately the same in developed and developing countries
- Only prevention is vaccination

Rotavirus: severe childhood gastroenteritis

- Most common cause of severe infectious diarrhoea and vomiting in young children worldwide^{1,2}
- Rotavirus infection is highly contagious¹
- Almost all children are exposed to rotavirus during the first few years of life²
- One of the leading causes of hospitalisation in young children in Australia and New Zealand, with the main complication being dehydration

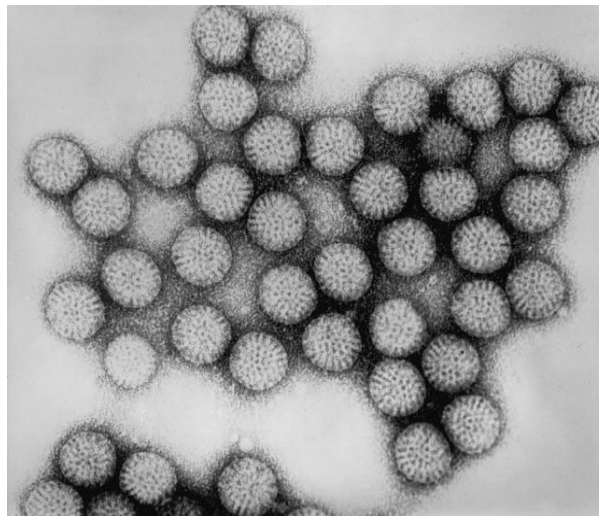


Image: Erskine Palmer, Centers for Disease Control and Prevention Atlanta, GA, USA

Parashar et al. Emerg Infect Dis 2003; Galati et al., Aust NZJ Public Health, 2006.

Viral transmission

- **Faecal-oral transmission:**
 - Readily transmitted from environmental surfaces, either directly or indirectly¹
 - Especially important in infants and young children, who frequently put their hands and toys into their mouths¹
 - Faecal matter from infected infants contains as many as 10^{10} particles /mL²
- **Droplet transmission?**
 - Universality of RVGE in children, regardless of hygiene levels or food and water quality^{3,4}
 - RV infection also associated with respiratory symptoms in humans^{3,4}



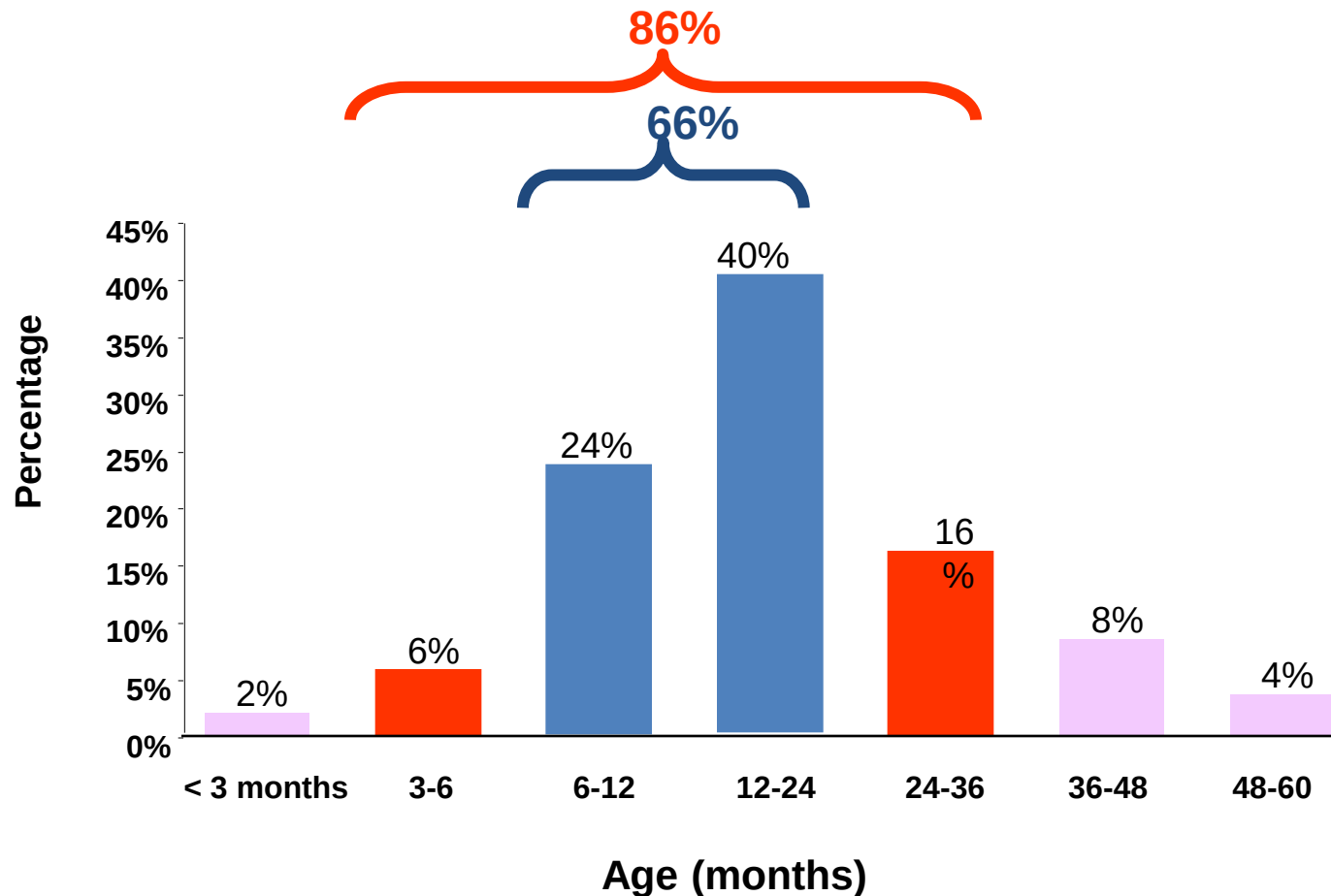
Rotavirus is a physically robust virus

- RV can survive on human hands for several hours^{1,2} and on non-porous inanimate surfaces for several days^{1,3}
 - Survives longest on non-porous surfaces in low-temperature, high-humidity environments³
- Relatively resistant to chemical disinfectants^{1,4,5}
 - Inactivated by relatively high concentrations of alcohol, chlorine or iodine^{6,7}

Standard sanitary measures are relatively ineffective in controlling rotavirus¹⁰

Nearly 90% of rotavirus gastroenteritis cases occur between 3 months and 3 years of age

Distribution of RVGE cases by age in all settings in Europe (2004-2005)

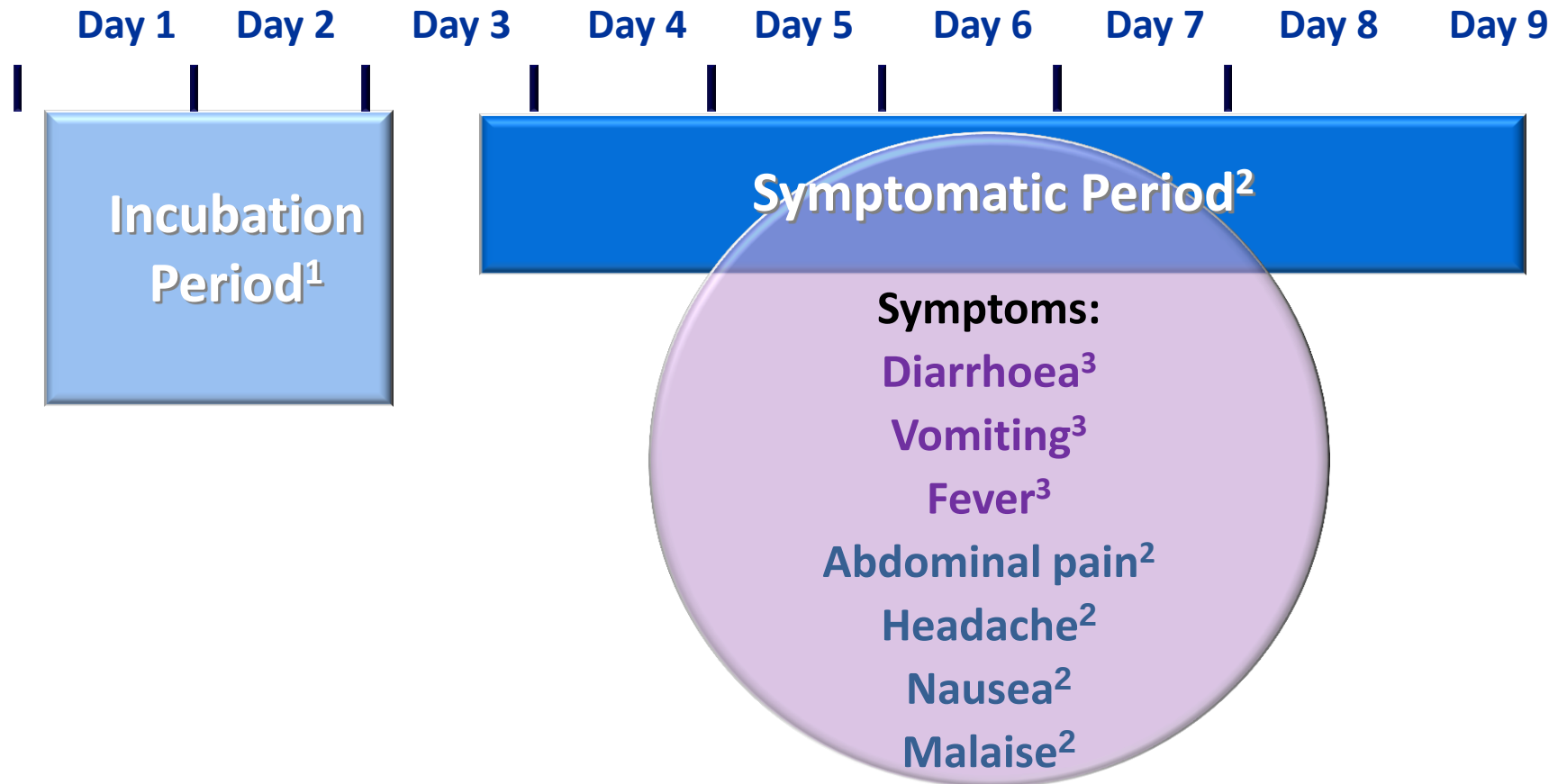


From REVEAL study¹: prospective, observational study of AGE in 2846 children <5 years of age seeking health care, in 2004–2005, in selected areas of 7 countries
Total AGE cases: 2 841

1. Van Damme P et al. J Infect Dis 2007;195(suppl 1):S4-S16.

2. REVEAL global report July 2007;SPMSD data on file.

Typical duration of rotavirus infection



Symptoms in purple are most commonly reported (63% of patients report all three)³
Symptomatic adults with rotavirus frequently report additional symptoms in blue²

1. Raebel MA and Ou BS. *Pharmacotherapy* 1999; **19**: 1279–95; 2. Anderson EJ and Weber SG. *Lancet Infect Dis* 2004; **4**: 91–9;
3. Staat MA et al. *Pediatr Infect Dis J* 2002; **21**: 221–7

Severe rotavirus gastroenteritis

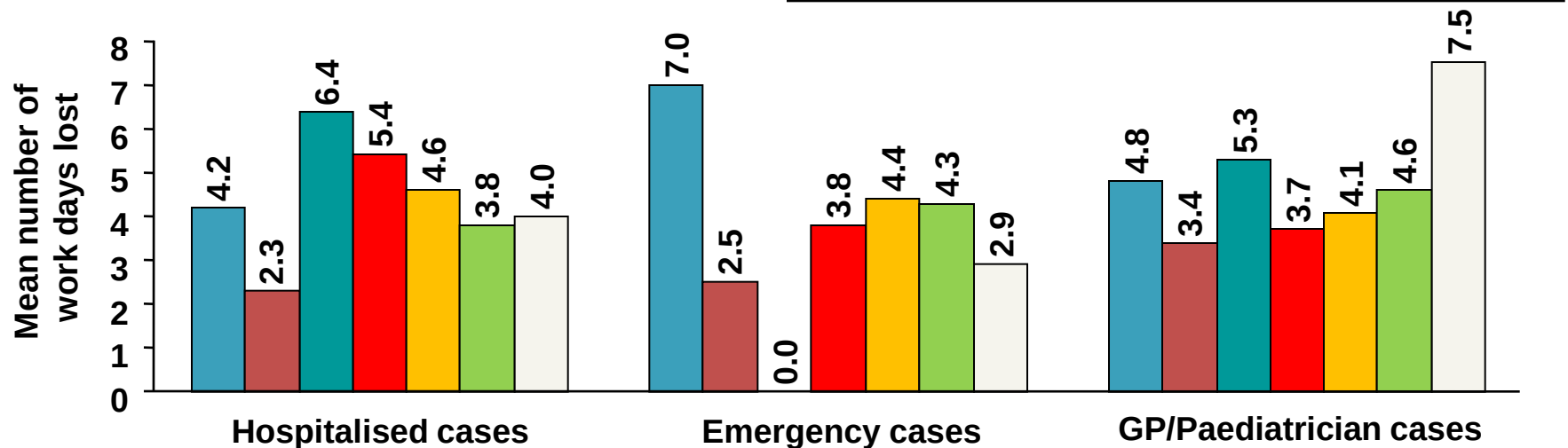
- RVGE can be severe enough to require hospitalisation in young infants and children¹
- RV infection is **unpredictable** with symptoms that include:²
 - severe diarrhoea
 - vomiting
 - fever
 - dehydration
 - electrolyte disturbances
 - shock



Image Service Urgences Pédiatriques Hôpital Armand Trousseau Paris

Average number of work days lost by parents due to their child being ill with RVGE

- Mean number of work days lost by parents due to child's RVGE in seven European countries
 - hospitalised cases: 4 days
 - emergency cases: 4 days
 - primary care cases: 5 days



Global Rotavirus burden

- 25 million clinic visits per year
- 2 million hospitalisations per year
- >527,000 deaths per year in children < 5 years (15% of deaths in children <5 yrs)
- Burden probably underestimated

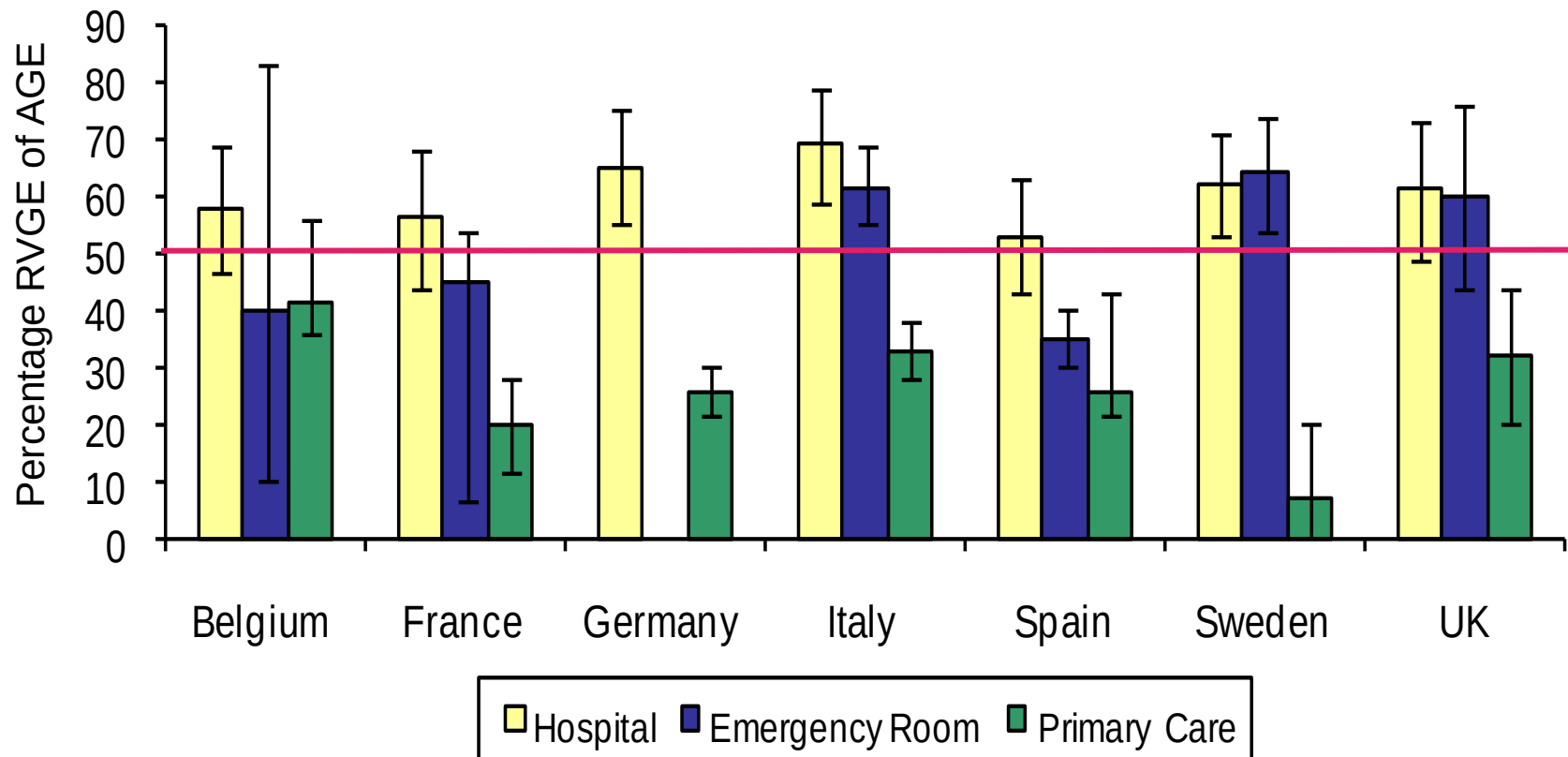
Rotavirus Epidemiology

Wealthy Countries

- Affects almost all children by 5 years of age with peak incidence in winter and spring
- 1 in 50 children hospitalised by age 5 years
- For each hospitalised child
 - 10 will visit GP and
 - 30 to 40 managed at home
- Rotavirus from stool 20-30% in Primary care
40-60% seen in Hospital with AGE

REVEAL study: percentage of RVGE among AGE cases in each study area stratified by setting

- More than 50% of hospitalisations for AGE are due to RV
- Around 30% of children seen in primary care for AGE have RV

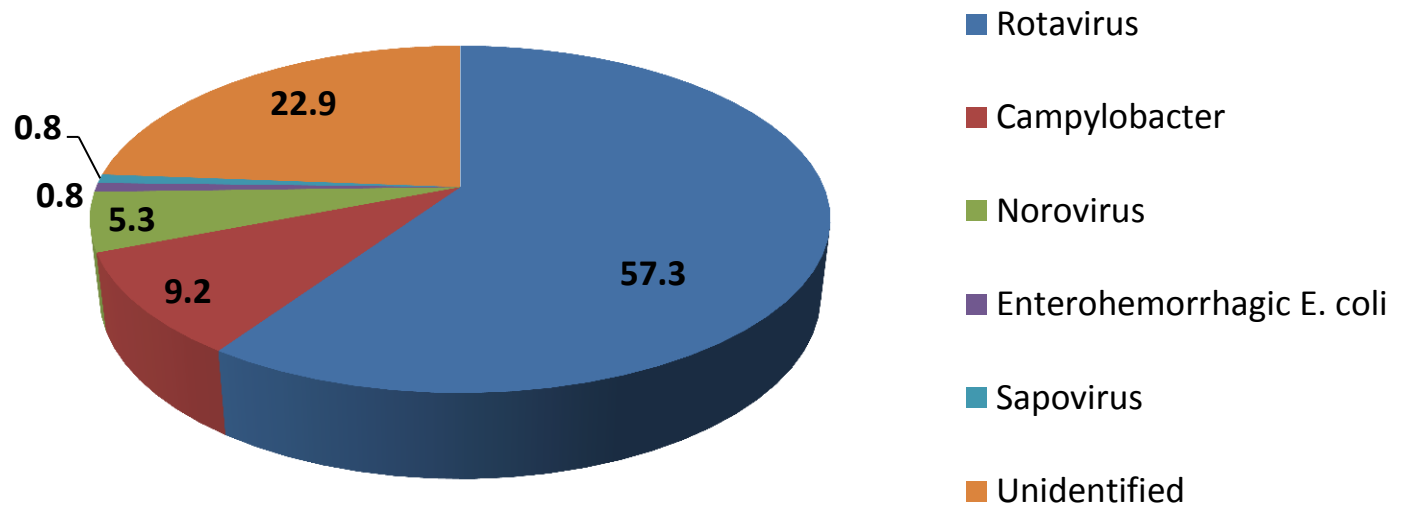


NZ Rotavirus Epidemiology

- Annually for those age less than 3 years
657 hospitalised/100,000
- Highest rate those aged 12 -23 months.
- One in 52 admitted by age 3 years
- One in 43 by age 5
- One in 5 will attend GP by age 5
- Rotavirus more likely to cause dehydration than other infections
- Peaks in winter when health burden at greatest

Rotavirus is the most common cause of severe gastroenteritis in NZ

- Rotavirus is the most common cause of GE resulting in hospitalisation of NZ children and is most severe in children aged <2 years¹



Rotavirus Hospital discharge data



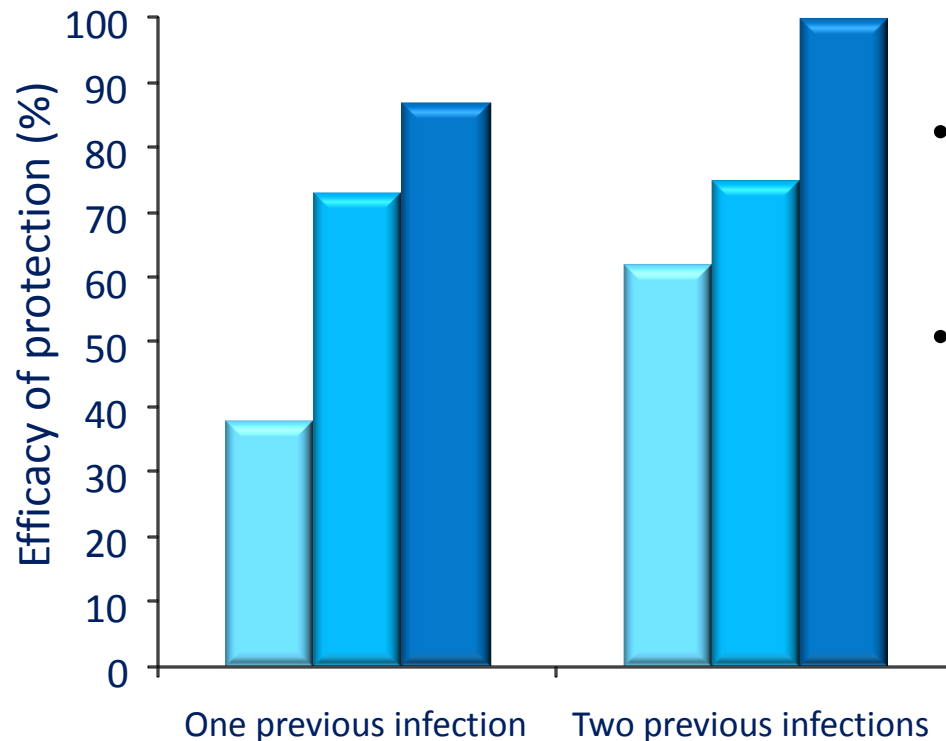
Licensed products

Protection from Infection

Rationale for vaccination

- Repeated infections throughout life but cumulative immunity provides broad protection
- Community study of Mexican infants
 - Initial (2nd) infection provided protection
 - 38% against asymptomatic infection (60%)
 - 73% against mild diarrhoea (83%)
 - 87% against moderate to severe illness (100%)

Natural immunity to rotavirus infection



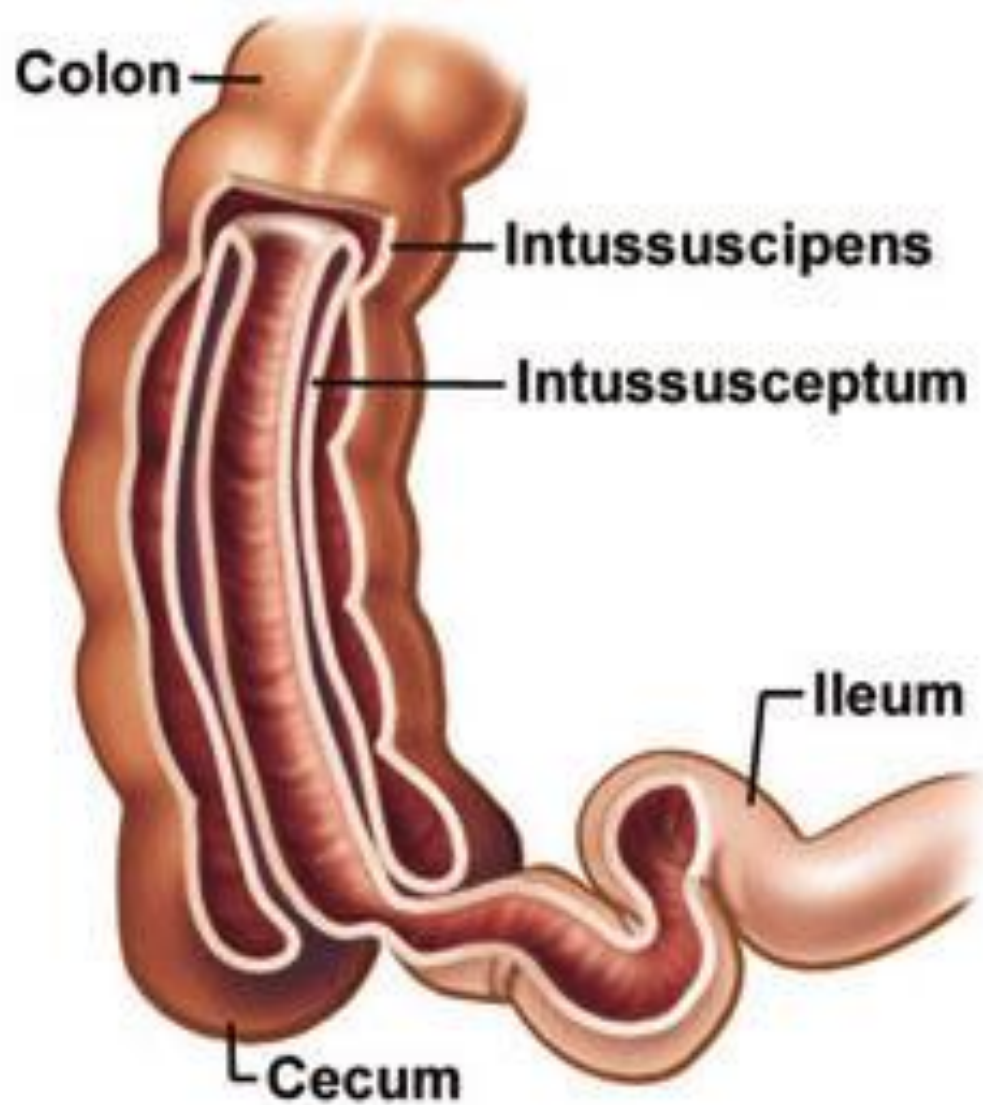
- Primary infection is usually the most severe
- Primary infection protects against subsequent infections (symptomatic and asymptomatic)
- Secondary infections are clinically milder or asymptomatic

■ Asymptomatic infection*
■ Mild diarrhoea
■ Moderate-to-severe diarrhoea

* no diarrhoea 5 days before or after detection of RV or during the interval in which a serological response detected

Rotavirus Vaccine history

- Rotashield – 1st rotavirus vaccine
- Highly efficacious
- Incidence of Intussusception in clinical trials
 - 5/10,054 vaccine recipients
 - 1/4,633 placebo recipients



RotaShield

- 10 months post licensure 15 cases reported to VAERS - 13 after first dose
- Vaccine use suspended - case control study - then vaccine withdrawn by company
- 1/10,000 - overall risk estimate

RR 1st dose - 37.27 ($P < 0.001$)

2nd dose - 3.8 ($P = 0.05$)

Risk highest when 1st dose after 3 months of age

RotaTeq (MSD)

- Human Bovine Pentavalent Reassortant Rotavirus Vaccine PRV
- 3 dose schedule, 6 -10 weeks apart starting from 6 weeks of age
- Rotavirus Efficacy and Safety Trial (REST): 68,038 infants from 11 countries - Europe, Latin America and USA
- Case definition for Rotavirus gastro
 - Subset monitored for all gastroenteritis
- Comprehensive safety monitoring

RotaTeq Safety

- Intussusception
 - 12 vaccine 15 placebo
- No case within 42 days receipt of vaccine
- Other adverse events similar frequency in vaccine and placebo group
 - Deaths 24 vaccine 20 placebo
 - SUDI 8 vaccine 7 placebo

RotaTeq Efficacy

- Severe disease
 - 94.5% (95%CI 90.5-98.2)
 - 2nd year 88% (95%CI 49.4-98.7)
 - all gastro hospitalisation 58.9% (95% CI 51.7-65.0)
- Faecal shedding 12.7% after dose 1,
nil after dose 2 or 3

Rotarix[®] GSK

- Monovalent human attenuated rotavirus vaccine G1P[8] - commonest strain
- Two dose schedule: first dose at age 6-14 weeks, second dose by age 24 weeks (minimum interval of 4 weeks between doses)
- Clinical efficacy trial: 63,225 infants 11 Latin American countries and Finland
- Case definition for Rotavirus gastro
- Comprehensive safety monitoring

Rotarix safety

- Intussusception
 - 9 vaccine 16 placebo
- Cases within 31 days either dose
 - 6 vaccine 7 placebo
- Fewer adverse events in vaccine compared to placebo group
 - Deaths - 56 vaccine 43 placebo
 - Excess pneumonia deaths in vaccine group but not within 31 days of immunisation
 - Note: no difference in serious Aes for pneumonia (280 vs 276) or pneumonia hospital admissions (277 vs 273)

Rotarix Efficacy

- Efficacy against severe disease in children up to age 1 year
 - Two doses - 85% (95% CI 72-92)
 - One dose - 81% (95% CI 71-87)

Studies in Asia and Western Europe also high efficacy

Studies in Africa efficacy around 60% (similar to Rotateq)

Summary: EFFICACY of Rotavirus vaccines

- The two currently licensed rotavirus vaccines, *human RV vaccine* and *bovine-human reassortant RV vaccine*, have undergone large-scale, worldwide clinical development programmes
- Both vaccines have demonstrated efficacy:
 - against RVGE, severe RVGE and RVGE-hospitalisations
 - against diverse rotavirus serotypes
 - sustained over the first few years of life
 - in co-administration with other routinely used infant vaccines
 - in challenging study settings in the developing world
 - in pre-term infants

***Rotarix* is generally well tolerated, with a similar rate of side effects to placebo^{1,2}**

- **Commonly reported side effects^{1,2}**
 - Diarrhoea
- **Rarely reported side-effects^{1,2}**
 - Flatulence, abdominal pain and dermatitis
- *Rotarix* was well tolerated in a study of 1,009 premature infants between 27 and 36 weeks gestation.²

Precautions for *Rotarix*: a live attenuated vaccine

- **Don't immunise** if child has:
 - Allergy to any of the components
 - Gut disorders: e.g. Hirschsprungs Disease, congenital malformations, past history of intussusception.
 - Severe Combined Immunodeficiency (SCID)
 - Is older than 24 weeks of age
- **Delay administration** if:
 - Fever/severe illness, especially vomiting/diarrhoea
- **Take further advice** if child is:
 - Known or suspected to be immunosuppressed
 - Receiving blood product or transfusion within 42 days
- **Advise routine hygiene precautions** if the child is in contact with an immunosuppressed person (not contraindicated)
- Vaccination recommended for premature babies according to chronological age (from 6 weeks) if clinically stable

What about intussusception?

- 2 large pre-licensure studies (each >60,000 children) showed no increase
- Population figures from active follow-up of intussusception cases in Australia found **NO OVERALL INCREASE** in intussusception after rotavirus vaccine but a slightly higher risk after the first dose
- Mexican population figures (*Rotarix*) suggest a slightly higher risk after the first dose overall but a similar study in Brazil did not demonstrate an overall risk
- Intussusception is a rare condition, with an annual incidence under 12 months of age in Australia of 80 per 100,000. The increased risk estimated at approximately 2 additional cases per every 100,000 infants vaccinated¹

1. <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-rotavirus>

Recommendations about intussusception¹

- As a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception
 - *Severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever.*
- Inform parents/caregivers of the *rare* risk of intussusception and advise them to promptly report such symptoms.
- Do not give rotavirus vaccine outside the recommended age limits or to an infant with any history of chronic gastrointestinal disease including uncorrected congenital malformation
- Report any cases of intussusception following rotavirus vaccination to CARM: carmnz@stonebow.otago.ac.nz
<https://nzphvc-01.otago.ac.nz/carm-adr>

Porcine Circovirus

- March 2010 DNA fragments from PCV in *Rotarix* subsequently found in *Rotateq*
- PCV present in seed stock
- Review of safety data of 100,000 trial subjects and post- licensure data from 100M infants
- Regulatory authorities recommend continued use
- Companies will remove fragments from vaccine

Cost benefit

- Depends on
 - Efficacy of vaccine
 - Cost of vaccine
 - Burden of disease - incidence and severity
-
- WHO suggests a cost effective intervention is one which averts a DALY at < 3 per capita GDP

Experience in other countries

- Post licensure data (introduced 2006) from USA suggest high efficacy and possible herd protection
- Aboriginal Australians high efficacy during outbreak
- Data from Australia indicates 75% reduction in hospitalisation in 2 years following introduction of vaccine
- Studies from Mexico (introduced 2007)
 - 41% reduction diarrhoea related deaths in vaccine recipients during 2008
 - 29% reduction in 1-2 year olds few of whom were vaccinated

Fit with Schedule

- *Rotarix* - 2 doses
 - First dose at 6 weeks - no later than 14 weeks
 - Minimum 4 week gap,
 - 2nd dose by 24 weeks
- *RotaTeq* - 3 doses
 - Start at 6 weeks - no later than 12 weeks
 - Minimum 4 week gap,
 - 3rd dose by 32 weeks
- **Great potential to improve on time coverage**

Rotavirus vaccine should be offered to infants because

- It should be on the schedule
- Rotavirus causes a serious illness in many children
- Parents lose time off work ~ 5 days
- Vaccine does "not" cause intussusception
- The pig virus does not cause illness in humans
- It is challenging because it has to be given by 12 or 14 weeks of age

Rotavirus vaccine summary

- No hesitation about recommending either
- Which one?

Questions for you

- Is there an obligation to inform parents of the availability of non schedule vaccines for their children?
- If so when? And how?
- How are parents to be informed about rotavirus vaccine in a timely manner? (first dose has to be administered by 12 (Rotateq) or 14 (Rotarix) weeks)

Suggested approach

- Send letter to pregnant women possibly in pregnancy pack covering routine schedule and non funded vaccines
 - Rotavirus, Varicella and cocoon pertussis
- Follow up phone call in 2nd/3rd trimester to discuss - offering appt. if required
- Sample letter can be provided

Excellent Summary Article

Grimwood K, Lambert SB, Milne RJ.
Rotavirus Infections and Vaccines
Pediatr Drugs 2010;12(4):1-22

Acknowledgements

- Colleagues on ITF and Ministry of Health who taught me so much
- Sharon Wong, Lesley Voss and David Graham who shared slides with me
- Colleagues at Ropata Medical Centre who critiqued this presentation

Rotarix product information

***Rotarix* is not currently available on the NZ National Immunisation Schedule**

Rotarix® (rotavirus oral vaccine) is available as a liquid suspension for ORAL administration, and contains not less than $10^{6.0}$ CCID₅₀ per 1.5mL dose. The vaccination course consists of two doses and should be completed by the age of 24 weeks. The first dose should be given between 6 and 14 weeks of age, with an interval before the second dose of at least 4 weeks.

Rotarix is a private-purchase prescription medicine for the prevention of rotavirus gastroenteritis – a prescription charge may apply.

Contraindications: Hypersensitivity to any component of the vaccine, or after previous administration of rotavirus vaccines; history of chronic gastrointestinal disease; uncorrected congenital malformation of the gastrointestinal tract (such as Meckel's diverticulum) that would predispose for intussusception; Severe Combined Immunodeficiency (SCID) disorder; or acute febrile illness.

Warnings and Precautions: *ROTARIX* SHOULD UNDER NO CIRCUMSTANCES BE INJECTED. *Rotarix* should be postponed in subjects suffering from diarrhoea or vomiting. Contacts of recent vaccinees should be advised to observe personal hygiene. Use with caution in infants with close contacts who are immunodeficient. As a precaution, healthcare professionals should follow up any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever), and advise parents/guardians to promptly report such symptoms. As with any vaccine, a protective immune response may not be elicited in all vaccinees. *Rotarix* does not protect against gastroenteritis due to other pathogens than rotavirus. The extent of protection that *Rotarix* might provide against rotavirus strains that have not been circulating in clinical trials is currently unknown.

Side effects may include diarrhoea, flatulence, abdominal pain, or dermatitis.

Before prescribing *Rotarix*, please review the full Data Sheet at www.medsafe.govt.nz.

Rotarix is a registered trade mark of the GlaxoSmithKline group of companies.

Marketed by GlaxoSmithKline NZ Limited, Auckland.

DA4311IG/11AP/149



UNATTENDED
CHILDREN
WILL BE GIVEN
AN ESPRESSO
AND A FREE PUPPY

The End

Varicella Vaccine

Rationale for Use

Stewart Reid

Arguments against varicella vaccination

- Its not severe enough
- Increase in mean age of infection leading to greater burden of disease
- Duration of immunity uncertain
- It costs too much
- Potential of vaccine to cause shingles
- Increase in shingles because of lack of boosting

Vaccine Schedule

- Reason not on schedule is Fiscal
- Strong case for including a varicella vaccine in childhood schedule and until it is on schedule offering it to many
- The impact of Chickenpox should not be underestimated

ITF considerations

- Disease and Epidemiology
- Licensed product(s)
- Experience in other countries
- Fit with immunisation schedule
- Cost benefit
- Surveillance

Disease and Epidemiology

The severity of chickenpox is underestimated

Varicella zoster virus

- Very infectious and mostly symptomatic
- Transmission is by respiratory route or contact with skin lesions
- Secondary attack rates in a household 70-90%
 - Infectious for 2 days prior to rash till vesicles crust over (about 7 days)
 - Incubation period 7-21 days
 - Subclinical disease occurs in about 5%
 - 2/3 of adults with no past history of chicken pox are immune

The illness

- Self limiting systemic infection
- Generalised pruritic rash
 - Rapid evolution of macule → papule → vesicle → crust
 - Presence of lesions in all stages
 - Wide variation in number of lesions
- Mild fever, malaise, anorexia
- Increased hepatic transaminase levels without jaundice
- Rarely thrombocytopenia and neutropenia

Complications

- Bacterial super infection
 - Group A beta haemolytic streptococci
- Central nervous system
 - Acute cerebellar ataxia - 1 in 4000 children <15 years
 - Encephalitis - 0.1-0.2%
 - Aseptic meningitis
 - Transverse myelitis
- Varicella pneumonitis
 - More common in adults and immunocompromised
- Arthritis, glomerulonephritis, myocarditis

Pregnancy and the Newborn

- Congenital varicella syndrome
- Fetal infection after maternal varicella during first or early second trimester
- <12 weeks gestation 0.4%
- 12-20 weeks 2%
- >20 weeks isolated case report

Congenital varicella syndrome

- Skin scars 78%
- Eye abnormalities 60%
- Limb abnormalities 68%
- Prematurity/ low birth weight 50%
- Cortical atrophy, mental retardation 46%
- Poor sphincter control 32%
- Early death 29%

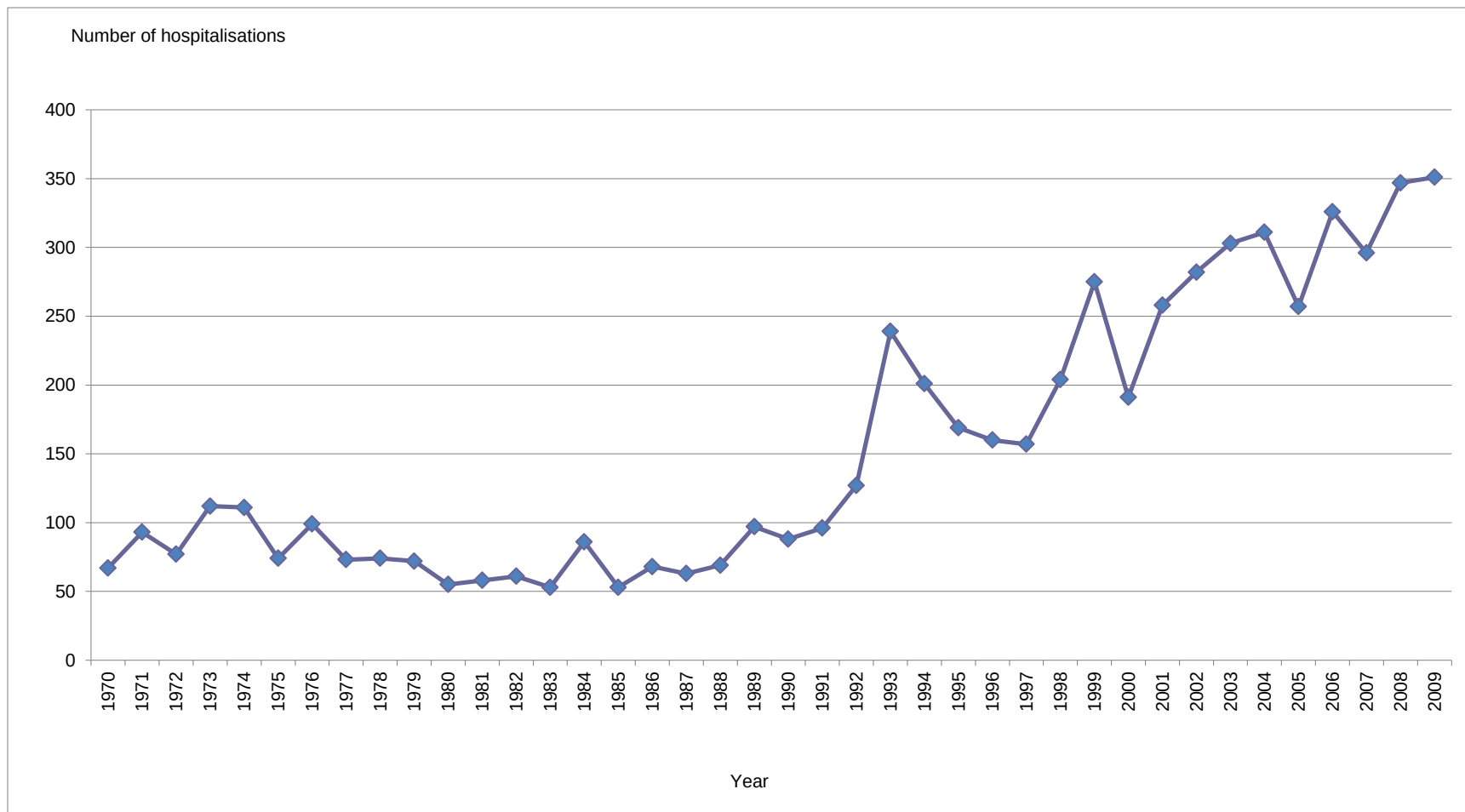
Pregnancy and the Newborn

- Varicella in mother
 - 7 days before to 7 days after delivery - infection can be fatal for infant
 - >5 days - disease severity modified
- Active maternal varicella around time of delivery
 - Varicella can develop 1-16 days of life in infants
 - Usual interval from onset of rash in a mother to onset in her neonate is 9-15 days

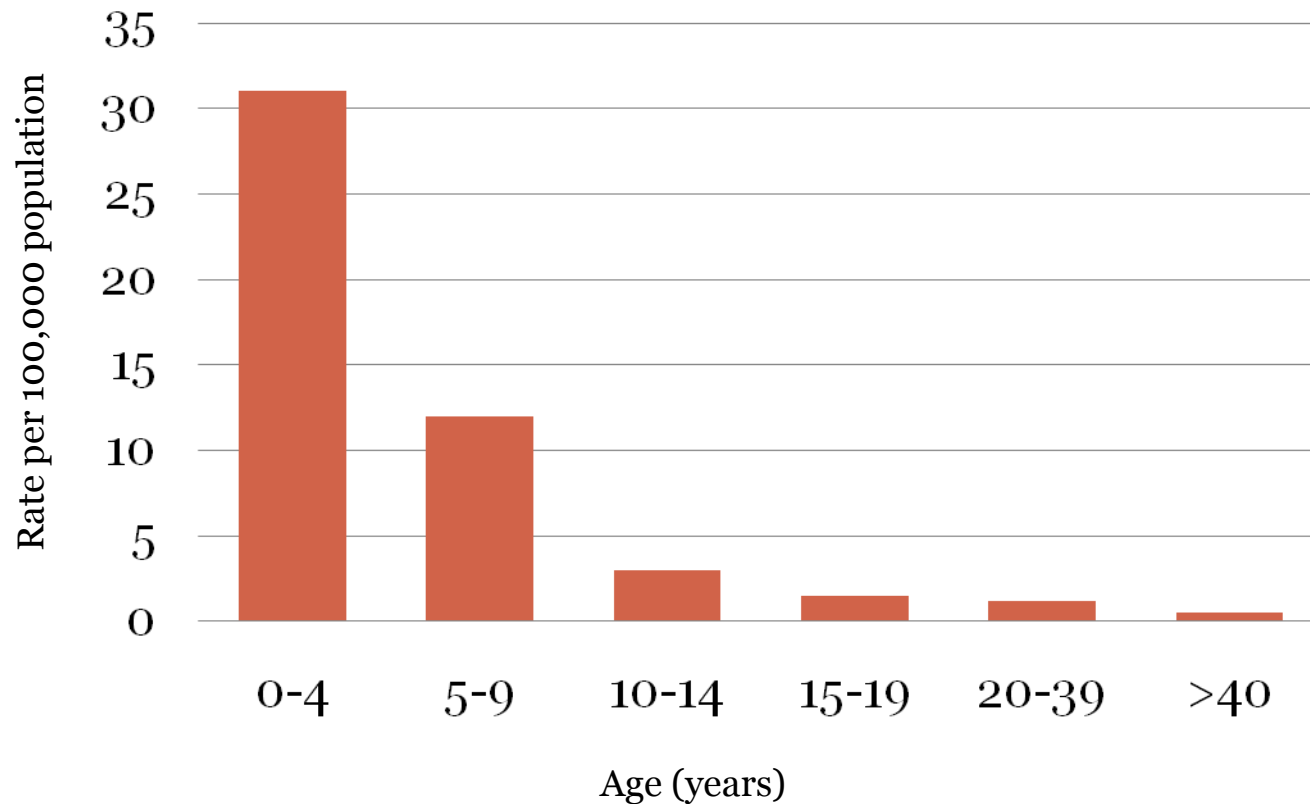
Varicella Epidemiology

- 3% infected as infants
- 90% infected by age 14 (7% - 8% per year on average) almost everyone (97%) by age 40
- Increase in hospitalisation for varicella from 50 - 100 (1970) per year to 300 + (2009) per year
- 1 death per year - similar rates to US and Australia
- ? Greater adult susceptibility with Asian Immigration

Varicella hospitalisations 1970-2009



Varicella Hospitalisation in New Zealand 1970-94



Hospitalisation

- Although majority of illness occurs in 5-9 yrs hospitalisation rates greatest for 0 - 4 yrs
31/100,000
- Underlying immune suppression only associated with 4% of hospitalisations
- About 1 death per year in NZ
- *But the problem with hospital discharge data...*

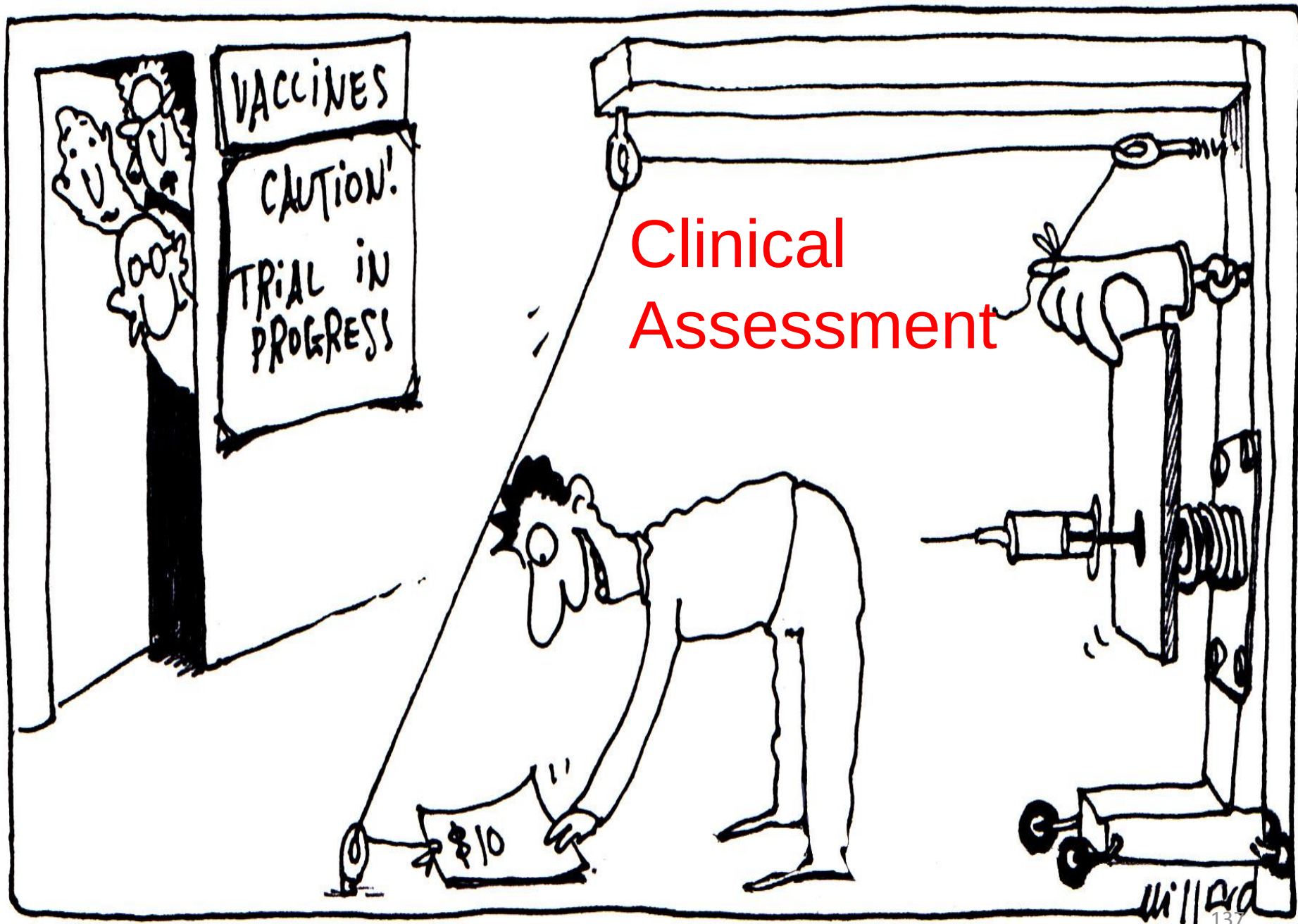
Starship chickenpox complications

July /August 2010

- 3 year old girl - osteomyelitis, pneumonia empyema,
- 8 year old girl - orbital cellulitis, subdural empyema, cavernous sinus thrombosis
- 8 week old boy - strep superinfection, multi-organ failure
- 3 year old girl - acute haemorrhagic infarct left basal ganglion
- 13 year old girl cerebellar ataxia followed by acute disseminated encephalomyelitis (ADEM)

- *Only one of the preceding 5 cases had chicken pox coded in discharge as secondary diagnosis*
- *So Chicken pox is not so benign!!*
- *With ~50,000 cases per year a low complication rate can result in a significant number of serious complications*

Licensed Vaccines



Clinical
Assessment

Vaccines

- Two single antigen - two MMRV
- Varilrix and PriorixTetra - GSK
- Varivax and Pro-Quad - MSD
- Only single antigen vaccines available at present

Vaccine efficacy

- Basic principle
 - Live viral vaccine given to susceptible children prior to exposure to wild type virus
 - Induces immunity to prevent primary infection and disease
 - Expect $\geq 95\%$ efficacy
 - Expect herd immunity - reduced transmission of infection and therefore reduction of disease in vaccinated AND unvaccinated people

Year of publication	Vaccine	Study design	Study setting	Vaccine effectiveness (estimate and 95% confidence interval)		
				All disease	Moderate or moderate/severe	Severe
1997 ¹³⁸	Varivax	Retrospective cohort	Child care centre outbreak	86% (73 to 92%)	100%	
1999 ¹³⁹	Varivax	Retrospective cohort	2 school outbreaks	71%, 100%	93%, 100%	
1999 ¹⁴⁰	Varivax	Prospective cohort	11 child care centres	84% (61–90%)	100%	
2001 ¹⁴¹	Varivax	Case control	Community clinical practice	85% (78–90%)		97%
2002 ¹⁴²	Varivax	Retrospective cohort	School outbreak	84%		
2002 ¹⁴³	Varivax	Retrospective cohort	Child care centre outbreak	79% (66–88%)	95%	
2002 ⁹³	Varivax	Retrospective cohort	Child care centre outbreak	44% (–6 to 67%)	86%	
2003 ¹⁴⁴	Varivax	Retrospective cohort	School outbreaks	85% (77–90%)	96% (88–99%)	
2004 ¹⁴⁵	Varivax	Case control	Community clinical practice	87% (81–91%)	98% (93–99%)	
2004 ¹⁴⁶	Varivax	Retrospective cohort	School outbreaks	72% (3–87%)		
2004 ³⁷	Varivax	Household contact	Households	79% (70–85%)	92%	100%
2004 ¹⁴⁷	Varilrix	Retrospective cohort	Health maintenance organisation	92% (91–93%)		
2004 ¹⁴⁸	Varivax	Retrospective cohort	School outbreak	56%	90%	
2005 ¹⁴⁹	Varivax	Retrospective cohort	School outbreak	89% (79–94%)	96% (88–99%)	100%
2005 ¹⁵⁰	Varivax	Retrospective cohort	School outbreak	87%		
2005 ¹⁵¹	Varilrix	Prospective cohort	8 child care centres	20% (0–40%)	93% (75–98%)	
2005 ¹⁵²	Varilrix	Case control	Community	88% (77–94%)	100%	
2006 ¹⁵³	Varivax	Retrospective cohort	School outbreak	82% (76–87%)	97% (94–99%)	

Table: Varicella vaccine effectiveness—summary of postlicensure studies

Vaccine Safety

- USA >55 million doses
- Reactions generally mild
- ~20% minor injection site reactions
- 3-5% localised rash
- Additional 3-5% generalised varicella-like rash
 - 2-5 maculo-papular lesions
 - Appear 5-26 post-immunisation

Vaccine Safety

- SAE reports rare
 - Anaphylaxis
 - Encephalitis, ataxia, seizures
 - Thrombocytopenia
 - Pneumonia
 - Erythema multiforme, Stevens-Johnson syndrome
- Most often in immuno-compromised children
- SAE frequency much lower than after natural infection

Experience in other countries

USA

US epidemiology pre-vaccine

- 4 million cases per annum
- 10,500 - 15,000 hospitalisation
- 100-150 deaths per year
- Risk of severe disease higher in adults but main burden born by children
 - 90% of cases and 67% of hospitalisation occur in children

US epidemiology post vaccination

- Vaccination commenced 1995
- Coverage 88% in children 19-35 months by 2005
- Resulted in
 - 71% - 84% reduction in varicella cases
 - 88% reduction in hospitalisation
 - 92% decrease in deaths

Impact of varicella vaccine in the USA

FIGURE 2. Varicella-related* hospitalization rates† among persons aged <50 years, by year and age group — United States, 1994–2002

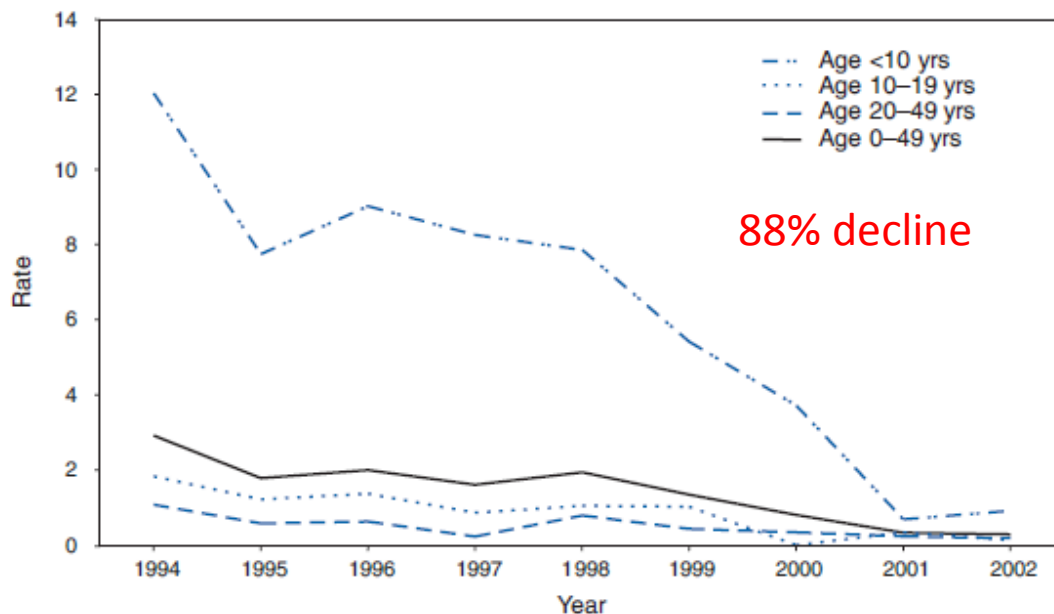
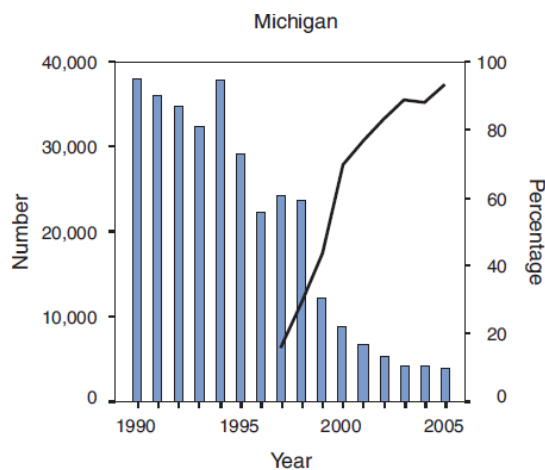
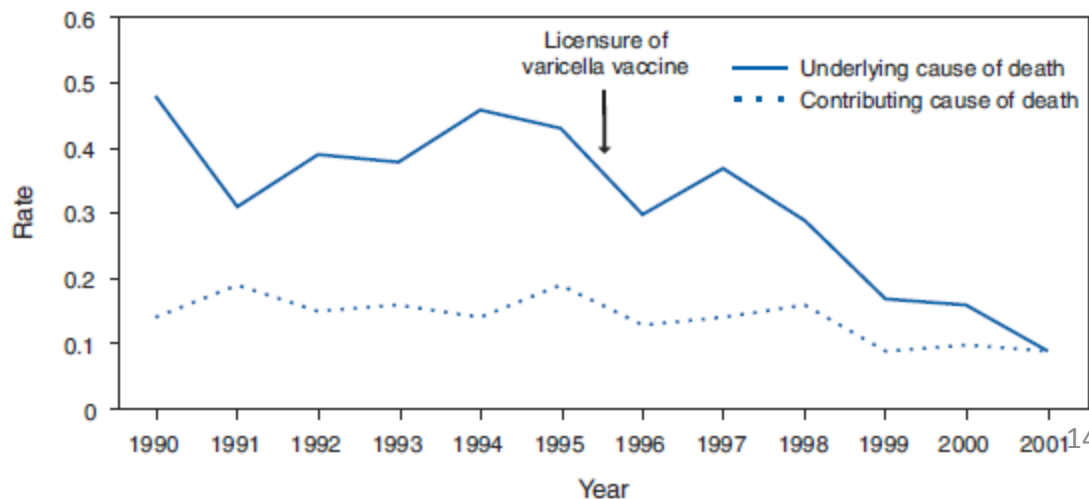


FIGURE 3. Varicella-related mortality rates,* by year and underlying and contributing cause of death — United States, 1990–2001



US epidemiology post-vaccine

- Incidence reduced by 57% to 95%, dependent on age
 - reduced by 90% in children <10 years of age
 - 80% decline in infants (ineligible for vaccination)
 - 74% decline among adults (low rates of vaccination)
- Peak age of infection shifted from 3-6 yrs → 9-11 yrs

US epidemiology post-vaccine

Outbreaks declined by 81%

- cases per outbreak declined from 15 to 9
- duration of outbreaks from 44.5 to 30 days
- age of outbreak cases increased from 6 to 9 years

Breakthrough varicella

- 15 to 20% of healthy vaccinated children will develop breakthrough varicella.
- Breakthrough disease mild, without fever and with fewer skin lesions
- Infectious - but less readily transmissible than varicella in unvaccinated persons
- Breakthrough disease account for majority of outbreaks now
- Argument for 2 dose schedule introduced USA 2007

Fit with Immunisation schedule

- One or two doses
- Problem with first dose - 15 month visit currently 3 injections
- Change MMR to MMRV and accept increased risk of febrile convulsions
- MMR + V - 4 injections at 15/12 or extra visit

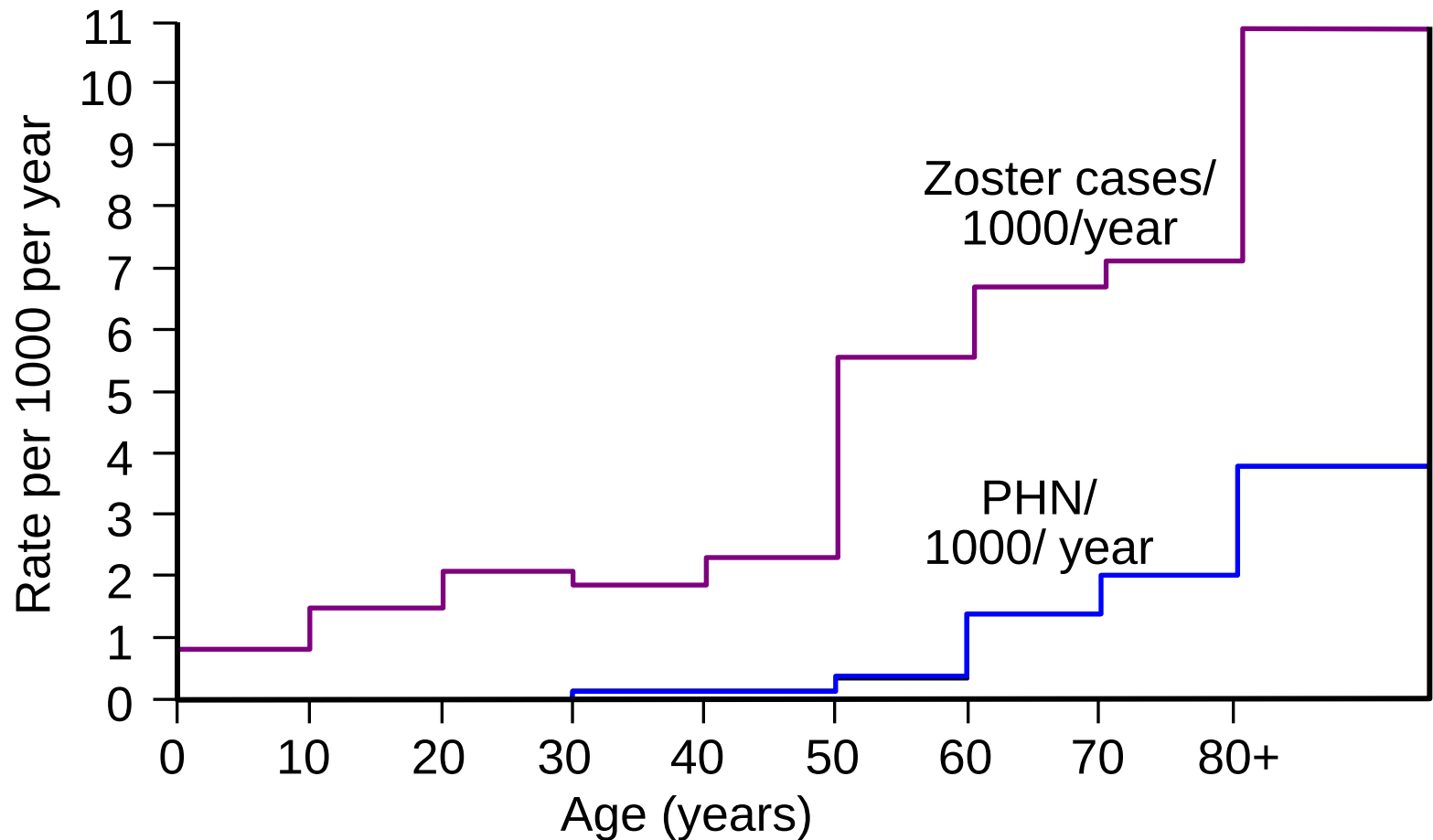
Cost effectiveness

- Economic cost - benefit analysis for NZ in 1999
- For every \$1 invested in immunisation programme
- Direct costs - \$0.67 return
- Indirect costs - \$2.79 return

Shingles and varicella vaccine

- The vaccine does become dormant in dorsal root ganglion and can cause shingles
- More likely if vaccinee suffers a rash
- Estimates to date indicate that it occurs less frequently than after wild virus

Incidence of Zoster and Postherpetic Neuralgia (PHN) in the United Kingdom



Shingles

Reactivation of VZV, risk reduced by external boosting of immunity through exposures to varicella or HZ, or both.¹

Case-control study²

- Risk of zoster lower (OR 0.29) among those exposed to 5 or more varicella cases compared to those without exposure
- Living with children was associated with a lower risk of zoster (OR 0.75)

Overall relationship between re-exposure to varicella and relative susceptibility to herpes zoster not clear

- e.g. women have a higher incidence of herpes zoster than men, but more likely to be exposed to young children with varicella

Shingles and vaccination

Varicella vaccination programme

- Mathematical models predict:
 - increased zoster incidence in the short term (10-40 yrs and up to 70 yrs)
 - lower incidence in the long term
- Post-vaccination surveillance:
 - no consistent trends
 - two studies found no change; two reported increased incidence (e.g. 3.2 cases per 1,000 person yrs in 1996-1997 → 4.1 cases in 2000-2001)

Zoster immunisation

- Zoster vaccine coverage expected to mask the effect of reduced rates of re-exposure.

Arguments against varicella vaccination

- Its not severe enough
- Increase in mean age of infection leading to greater burden of disease
- Duration of immunity uncertain
- It costs too much
- Potential of vaccine to cause zoster
- Increase in zoster because of lack of boosting

Varicella vaccine should be offered to children because

- It should be on the schedule
- Chickenpox is not a mild illness
- Vaccine saves money on societal basis
- Vaccine will increase average age of infection but at much overall lower rate
- Vaccine has not resulted in an increase in shingles and for all the concerns the USA is our guinea pig

Talking with parents about vaccinating children against varicella

For whom should we recommend vaccine?



Who should get Varicella vaccine?

- Discuss with all parents at 15 months (or earlier) but in particular for:
 - Toddlers heading off to communal living (daycare)
 - Any chronic condition which might be exacerbated by secondary bacterial sepsis
 - Skin (eczema)
 - Respiratory
 - Neurologic..?
 - Renal disease

Who should get Varicella vaccine?

High Risk

Individuals in a household with an immune compromised patient ('ring fence')

Children due to have solid organ transplants

Others

Susceptible adults/adolescents in particular

- health care workers,
- those born in tropical countries
- women planning families
- teens heading off to communal living (along with meningococcal vaccine and Tdap)

Who must not get varicella vaccine?

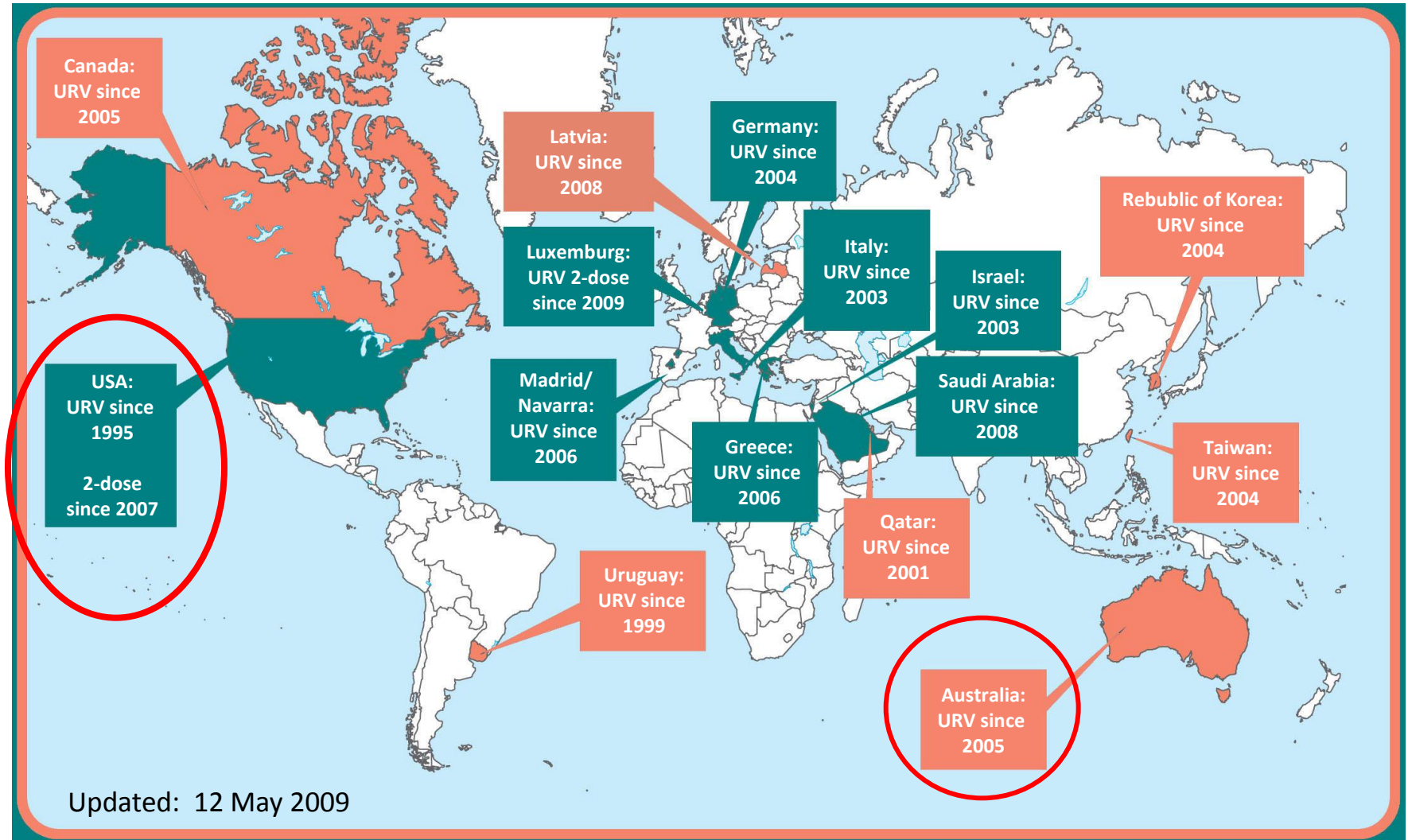
Anyone who shouldn't get a live virus vaccine - i.e. Severely immune compromised individuals

Pregnant women

Vaccine dosing schedule

- From 9 months (*Varilrix*) or 12 months (*Varivax*)
- Live attenuated vaccines, from Japan Oka strain
 - administer at the same time or ≥ 1 month before or after another live virus vaccine (e.g. MMR)
- One or two doses?

Countries using one-dose and two-dose schedules for *Varilrix*®



Summary

- The impact of Chicken pox is significant
- Strong case for varicella vaccination which is effective and safe
- Communicate with mothers about immunisation during pregnancy
- Offer Varicella vaccine with MMR at 15 months

Acknowledgements

- Colleagues on ITF and Ministry of Health who taught me so much
- Sharon Wong, Lesley Voss and David Graham who shared slides with me
- Colleagues at Ropata Medical Centre who critiqued this presentation

Questions for you

- Is there an obligation to inform parents of the availability of non schedule vaccines for their children?
- If so when? And how?
- How are parents to be informed about rotavirus vaccine in a timely manner? (first dose has to be administered by 12 or 14 weeks)
- Will you recommend varicella vaccine as a fourth injection at 15 months or suggest another visit?

***Varilrix* product information**

***Varilrix* is not currently available on the NZ National Immunisation Schedule**

Varilrix® (live attenuated varicella vaccine) is available as an injection, 0.5mL per dose. *Varilrix* is a private-purchase medicine – a prescription charge will apply. Prescription Medicine for the immunisation and prophylaxis against varicella in adults and children older than nine months. Contraindications: acute severe febrile illness, lack of cellular immunity, known systemic hypersensitivity to neomycin, or pregnancy. Pregnancy should also be avoided for three months after vaccination. Precautions: ensure medical treatment is readily available in case of rare anaphylactic reaction following administration; use caution in immunocompromised patients or those under immunosuppressive treatment; do not administer intradermally or intravenously. Avoid salicylates for 6 weeks after vaccination. Common side effects include local reactions such as pain, redness and swelling at the injection site; other reported reactions include small numbers of papulo-vesicular eruptions or a low-grade fever. Before prescribing *Varilrix*, please review the full Data Sheet at www.medsafe.govt.nz. *Varilrix* is a registered trade mark of the GlaxoSmithKline group of companies. Marketed by GlaxoSmithKline NZ Limited, Auckland. TAPS DA1611AH/11MY/XXX



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The End

Pertussis Control in New Zealand

How can we do better?

Pertussis Control in New Zealand

- The vaccination schedule
 - How we got there. Is it ideal?
- How we are performing?
 - What do we need to do to improve?
- What new strategies exist to better control pertussis?

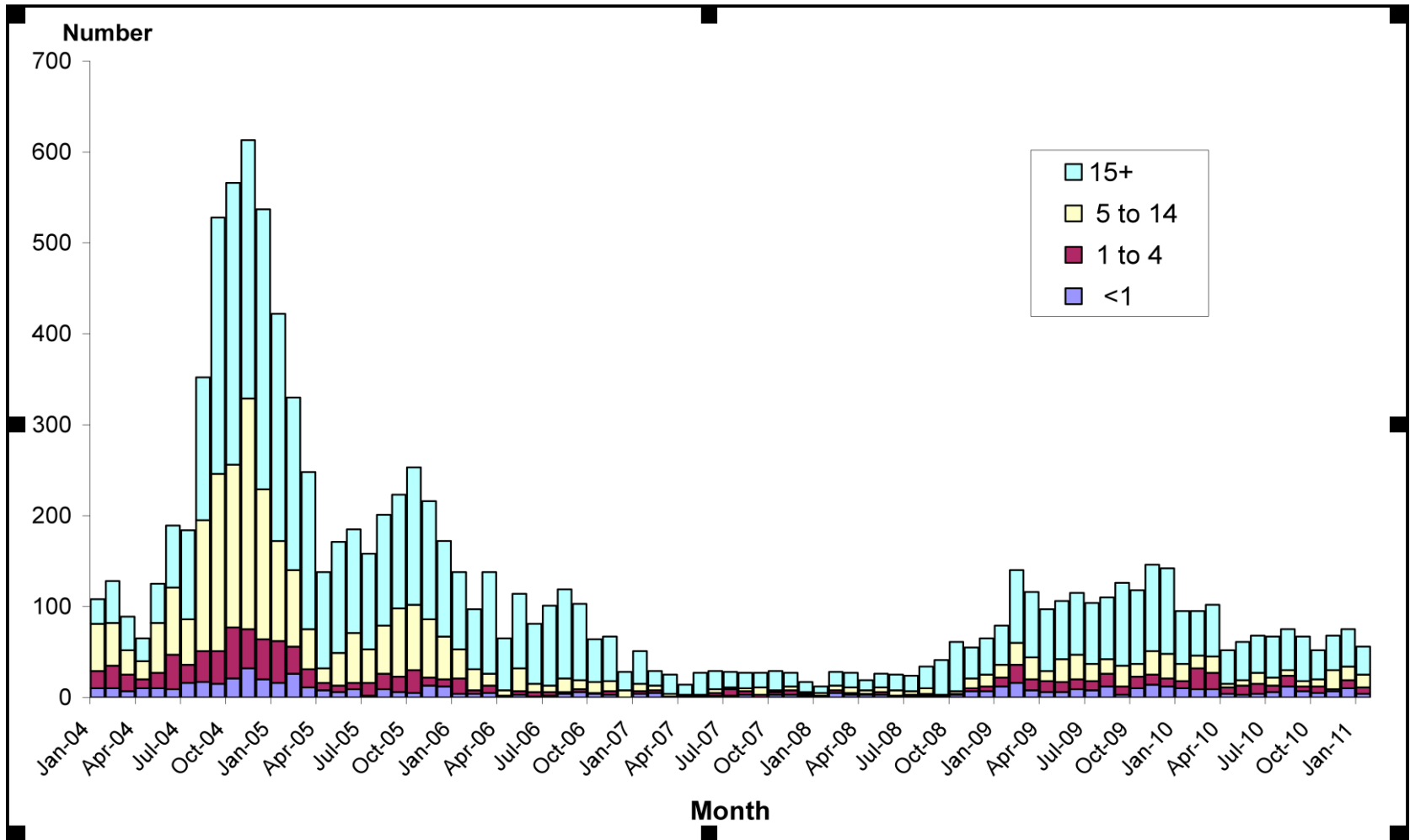
Two issues of Importance

- Pertussis immunity is not life long
- High vaccination coverage alone will not protect infants.

2011 NZ Childhood Schedule

	Conjugate Pneumo	Hexavalent DTaP-IPV- Hib HepB	MMR	Hib	DTaP- IPV	Tdap
6weeks	X	X				
3months	X	X				
5 months	X	X				
15 months	X		X	X		
4 years			X		X	
11 years						X HPV 3 doses ¹⁷²

Pertussis notifications 2004 - 10



NZ Immunisation coverage and timeliness at age 1 year



5 fold increased risk of an infant being hospitalised with pertussis if any of the three doses of the primary infant immunisation series are delayed

Grant CC, et al. Delayed immunisation and risk of pertussis in infants: unmatched case-control study.
BMJ 2003;326:852-3

Immunisation Timeliness

- For Pertussis the Target must be -
- "three doses of pertussis containing vaccine by 6 months of age"

Global pertussis initiative: Pertussis control strategies

1. Reinforce and/or improve current infant and toddler immunisation strategies
 - Direct protection
2. Create a cocoon of contacts who are immunised and hence less able to spread pertussis to infants
 - Indirect protection

Global pertussis initiative:

Seven pertussis control strategies

1. Reinforce and/or improve current infant and toddler immunisation strategies
2. Universal preschool booster doses at age 4-6 years
3. Universal adolescent immunisation
4. Universal adult immunisation
5. Selective immunisation of new mothers, family, and close contacts of newborns
6. Selective immunisation of health care workers
7. Selective immunisation of child care workers

Cocoon Immunisation

- Families of newborns
- Health care workers
- Childcare workers

How frequent is pertussis in adults?

Relative proportion of pertussis in adults -cough >7days

•	USA	Strebel et al 2001	10%
•	USA	Nennig et al 1996	12%
•	USA	Wright et al 1998	16%
•	USA	Mink et al 1992	13%
•	Can	Senzilet et al 2001	20%
•	DK	Birkebaek et al 1999	17%
•	F	Gilberg et al 2002	32%
•	UK	Miller et al 2001	28%
•	D	Riffelmann et al 2006	10%

Pertussis – Who infects infants?

~50% source not identified – all studies

- F Baron et al 1998 Hospitalised infants –
34% parents, 46% sibs
- D Kowalzik et al 2003 Infants in ICU –
46% adults mostly mothers
- GB Crowcroft et al Infants mostly in ICU –
43% parents 27% vaccinated sibs
- USA Bisgard et al 2004 Infants <4 months notified cases
35% mothers, 14% fathers , 8% grandparents
- Can, D, F, USA Wendelbore et al 2007 Hospitalised infants
55% parents mostly mothers, 16% siblings,
28% other adults in household

Pertussis - Sources of infection in infants

- Parents (Mothers particularly)
- Siblings
- Other adults in household

Selective immunisation of new mothers, family, and close contacts of newborns

Birth of a child should be the trigger for ensuring all children and adolescents have received scheduled immunisations and boosters are offered to all other household members

Cocoon Immunisation

- Families of newborns
- Health care workers
- Childcare workers

Selective immunisation of health care workers

- Health care workers are at increased risk of pertussis
- Outbreaks in maternity wards, neonatal units and in outpatient settings
- Fatalities occur as a result
- Benefit for the hospital is estimated to be 2.4 times the dollar amount spent on vaccinating health care workers

Staff immunisation logistics

- Pertussis epidemics are long
 - Approx 18 months
 - Staff turnover
- Staff identification and capture!
- Priority is staff in neonatal and paediatric intensive care units, emergency department, general paediatric wards, paediatric cardiology, all those working in obstetrics.
 - Other relevant healthcare workers include
 - GP's and practice nurses
 - Providers of well-child services

Strategy	Do we have it?	How well do we do it?
Primary series	Yes	Not well enough
4 year booster	Yes	Don't know
Adolescent immunisation	Yes	Don't know
Universal adult immunisation	No	Probably not
Immunisation of new mothers, family, and close contacts of newborns	No	But we should
Selective immunisation of health care workers	Yes, some DHBs	Don't know
Selective immunisation of child care workers	No	Possibly in the future

How soon after Td can Tdap be given?

- The Immunisation Handbook 2006 states - two years
- Derived from Canadian studies showing no increase in adverse event for those vaccinated 18-23 months after Td^{1,2,3}
- Some authorities recommend a much shorter time interval for healthcare personnel with direct patient contact³

Canadian recommendations

- In the context of catch-up programs, because of the vulnerability of this group to pertussis the pertussis booster (Tdap) should not be delayed for fear of adverse events related to the diphtheria or tetanus toxoid component, regardless of the elapsed time since the previous diphtheria and tetanus toxoid-containing vaccine.

Summary

- Achieve 95% coverage for all five schedule doses with on time coverage particularly for the first three doses
- Immunise family/household contacts of newborns, particularly mothers
- Immunise healthcare workers dealing with children particularly those who treat sick infants

Thank you for your attention

- Acknowledgments and thanks
- Cameron Grant,
- Diana Lennon
- Mark Thomas
- Elizabeth Wilson



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The End

Likely benefits of two doses vs one dose

- Further decrease varicella incidence and complications¹
- Reduce the number of individuals susceptible to varicella²
- Provide greater protection against breakthrough varicella²
- Lower the frequency of outbreaks²
- Decrease circulation of wild-type VZV
- Increase duration of protection

Breakthrough varicella

In 2005 with active surveillance

- 57-64% of reported varicella cases were due to breakthrough disease
 - Rate of spread of wild-type VZV from children with breakthrough disease to vaccinated contacts was 12-73%
 - Vaccine recipients aged 8-14 yrs twice as likely to develop moderate breakthrough varicella as those aged 1-7 yrs.
 - Waning of immunity after single dose?
 - Probably combination of waning immunity and primary vaccine failure
- argument for a 2-dose schedule for children

Global pertussis disease burden

1. 300,000 deaths per year
2. 50 million cases in children worldwide each year
3. Disability-adjusted life years in 2000
 - Pertussis 12.7 million
 - Lung cancer 11.4 million
 - Meningitis 5.8 million

Disability adjusted life years = years of life lost + years lived with disability

Pertussis Vaccination History in New Zealand-1

- 1960 - 3 doses un-adjuvanted vaccine as DTPw at 3, 4 and 5 months of age
- 1971 - changed to two doses of alum adjuvanted vaccine at 3 and 5 months
- 1982 large pertussis epidemic with several deaths

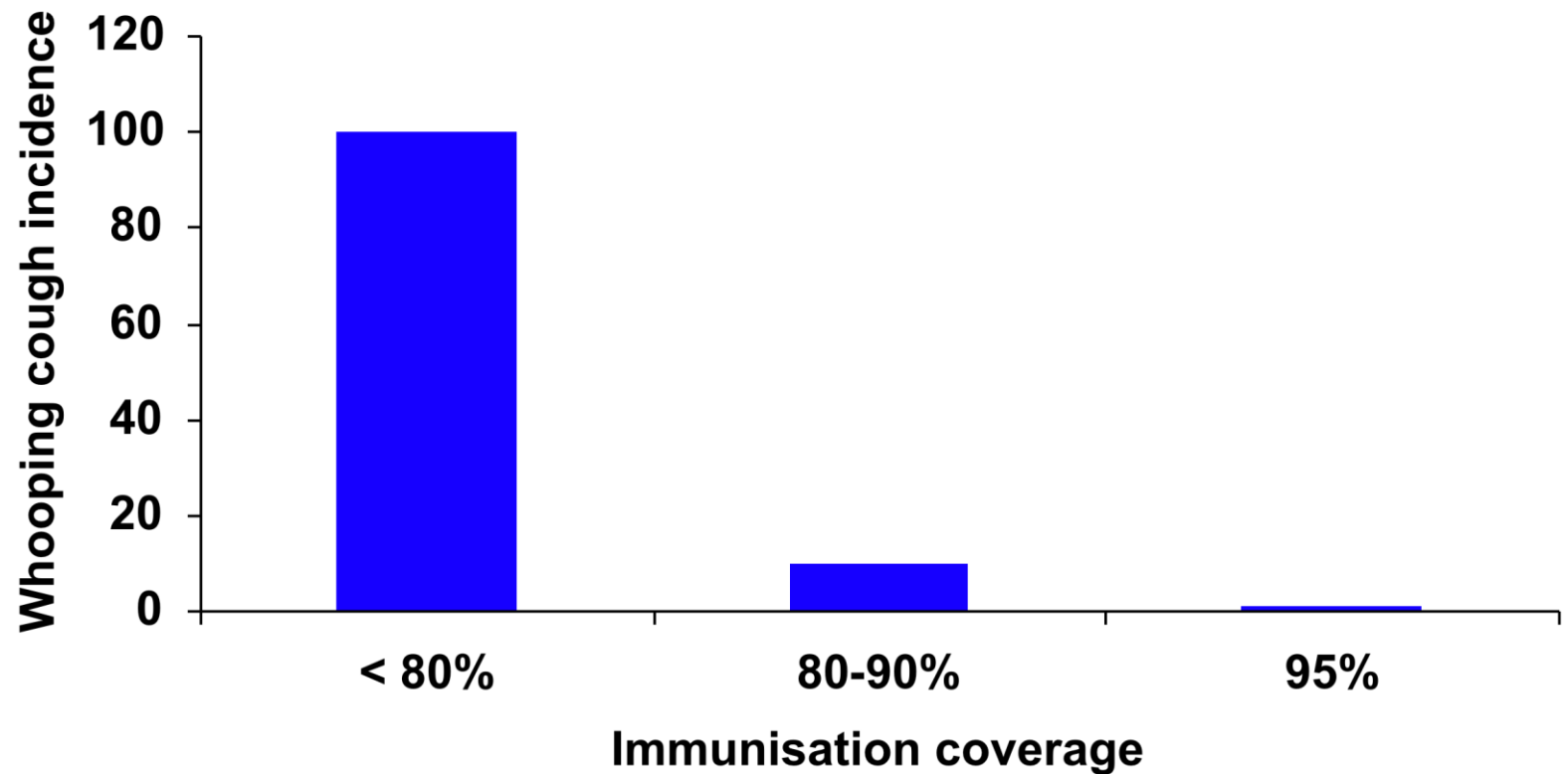
Pertussis Vaccination History in New Zealand-2

- 1984 -Increase from two to three doses
 - because the two dose schedule at 3 and 5 months was inadequate
 - Two decisions - extra dose and when to be administered
- NZ unique primary immunisation schedule
 - 6 weeks 3 months 5 months

Pertussis Vaccination History in New Zealand -3

- Three to four doses -1996
- Change to acellular pertussis vaccine - 2000
- Four to five doses - 2002
- Adolescent dose - 2006

To control pertussis you have to do
immunisation well



New Zealand Coverage

- At age 2 years
 - 60% in 1992 -
 - 77% in 2005 -
 - 85% in 2009
 - Now 90%
-
- Significant ethnic differences and large variability between DHBs
 - 66% - 90% at 12 months
(NIR data for year ending 2009)

Protection from Infection

Rationale for vaccination

- Repeated infections throughout life but cumulative immunity provides broad protection
- Community study of Mexican infants
 - Infection provided protection

	1 st infection	2 nd infection
Asymptomatic infection	38%	60%
Mild diarrhoea	73%	83%
Moderate to severe illness	87%	100%

Boostrix[®] product information

Boostrix[®] (combined diphtheria-tetanus-acellular pertussis (dTpa) vaccine) is available as an injection. A 0.5 mL dose contains not less than 2.5 LfU of diphtheria toxoid, not less than 5 LfU of tetanus toxoid, 8mcg of PT, 8 mcg of FHA, and 2.5 mcg of 69 kDa OMP. *Boostrix* is a private-purchase Prescription Medicine for booster vaccination against diphtheria, tetanus, and pertussis of individuals aged 10 years and older – a prescription charge will apply. **Contraindications:** known hypersensitivity to any component of the vaccine, encephalopathy following previous pertussis vaccination, or transient thrombocytopenia or neurological complications following earlier immunisation against diphtheria and/or tetanus. **Precautions:** do not administer intravenously; ensure medical treatment is readily available in case of rare anaphylactic reaction following administration. **Common side effects** include malaise, fatigue, headache, irritability, loss of appetite, and diarrhoea, and local reactions such as pain, redness, and swelling at the injection site. Very rarely reported reactions include allergic reactions such as anaphylactoid reactions. Before prescribing *Boostrix*, please review the Full Data Sheet at www.medsafe.govt.nz. *Boostrix* is a registered trade mark of the GlaxoSmithKline group of companies. Marketed by GlaxoSmithKline NZ Limited, Auckland.

Questions



Thank you for your attendance

Please complete your evaluation forms

