



Changes to the NZ Schedule for 2017

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Sep 2016



From 1st January 2017

- HPV

- Funded for males and females up to 26 years old
- 2 dose schedule for those 14 years and under
- 3 dose schedule for those 15 – 26 years
- 4 valent vaccine (Gardasil) will be replaced with the 9 valent vaccine (Gardasil 9)

From 1st July 2017



- VARICELLA

- Varilrix vaccine will be funded for one dose at 15 months old
- Catch up programme in General Practice for 11 year olds who are unvaccinated or have not had chickenpox
- Funding criteria for high risk groups will stay the same

From 1st July 2017 cont...

- PNEUMOCOCCAL

- 13 valent vaccine (Prevenar 13) will be replaced with the 10 valent vaccine (Synflorix)
- Prevenar 13 will be available for high risk groups only (followed by Pneumovax23)

- HIB

- Act-HIB brand vaccine will be replaced with the Hiberix brand



From 1st July 2017 cont.

- ROTAVIRUS

- RotaTeq brand vaccine will be replaced with the Rotarix brand
- 3 dose will be replaced with a 2 dose schedule

- MMR

- MMR-II brand vaccine will be replaced with the Priorix brand

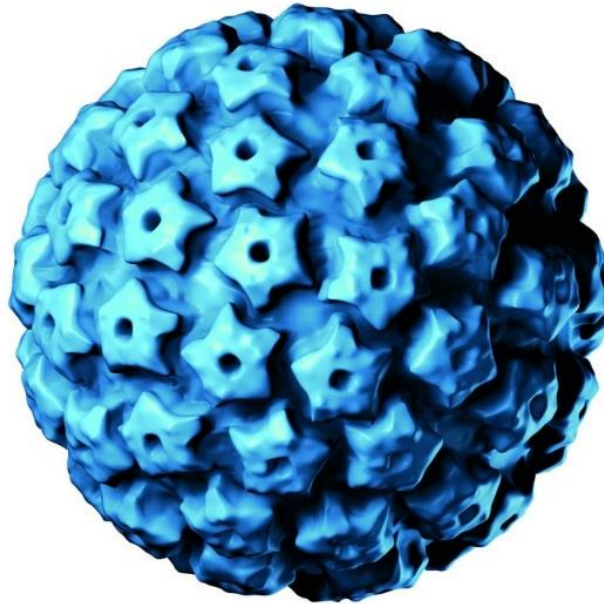


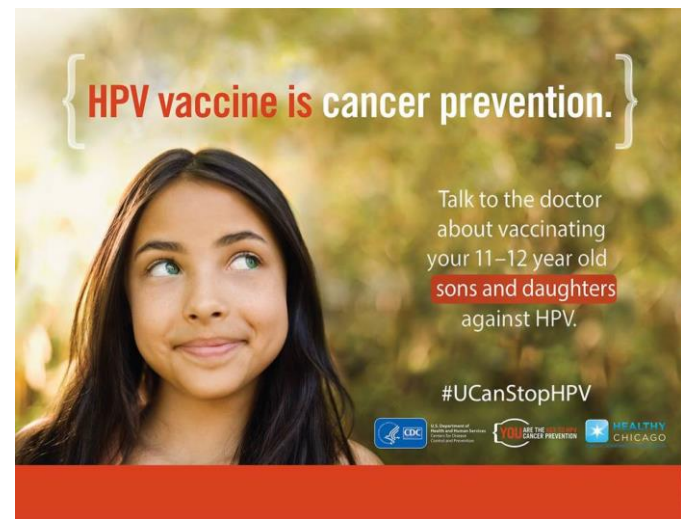


HPV Vaccination: Introduction of HPV9 for boys and girls

Ref: 2016 Academic Review for the New Zealand National
Immunisation Schedule: Human papillomavirus
DRAFT IMAC Aug 2016

- >140 types of HPV
 - 30 – 40 affect the genital areas
 - Approx 12 are oncogenic
- Most HPV infections are cleared within 18 months
 - Clearing an infection does not necessarily lead to immunity
 - Reinfection is possible





- HPV4 covers approx. 70% of oncogenic types leading to cervical cancer
- HPV9 expected to cover approx. 87%
 - 6,11,16,18
 - PLUS 31,33,45,52,58
- First licensed in US in 2014
- Licensed in Europe in 2015

HPV4 vaccine (Gardasil, Seqirus/MSD) contains:

- 40 µg of HPV16 L1 VLP, 20 µg of HPV18 L1 VLP, 20 µg of HPV6 L1 VLP and 40 µg of HPV11 L1 VLP
- 225 µg of aluminium hydroxyphosphate sulphate.



HPV9 vaccine (Gardasil9, Seqirus/MSD) contains:

- 30 µg of HPV6 L1 VLP, 40 µg of HPV11, 60 µg of HPV 16, 40 µg HPV18, 20 µg of HPV 31, 33, 45, 52 and 58
- 500 µg of aluminium hydroxyphosphate sulphate.

No preservatives or antibiotics

Also contain sodium chloride, L-histadine, polysorbate, sodium borate, traces of yeast protein, water for injection



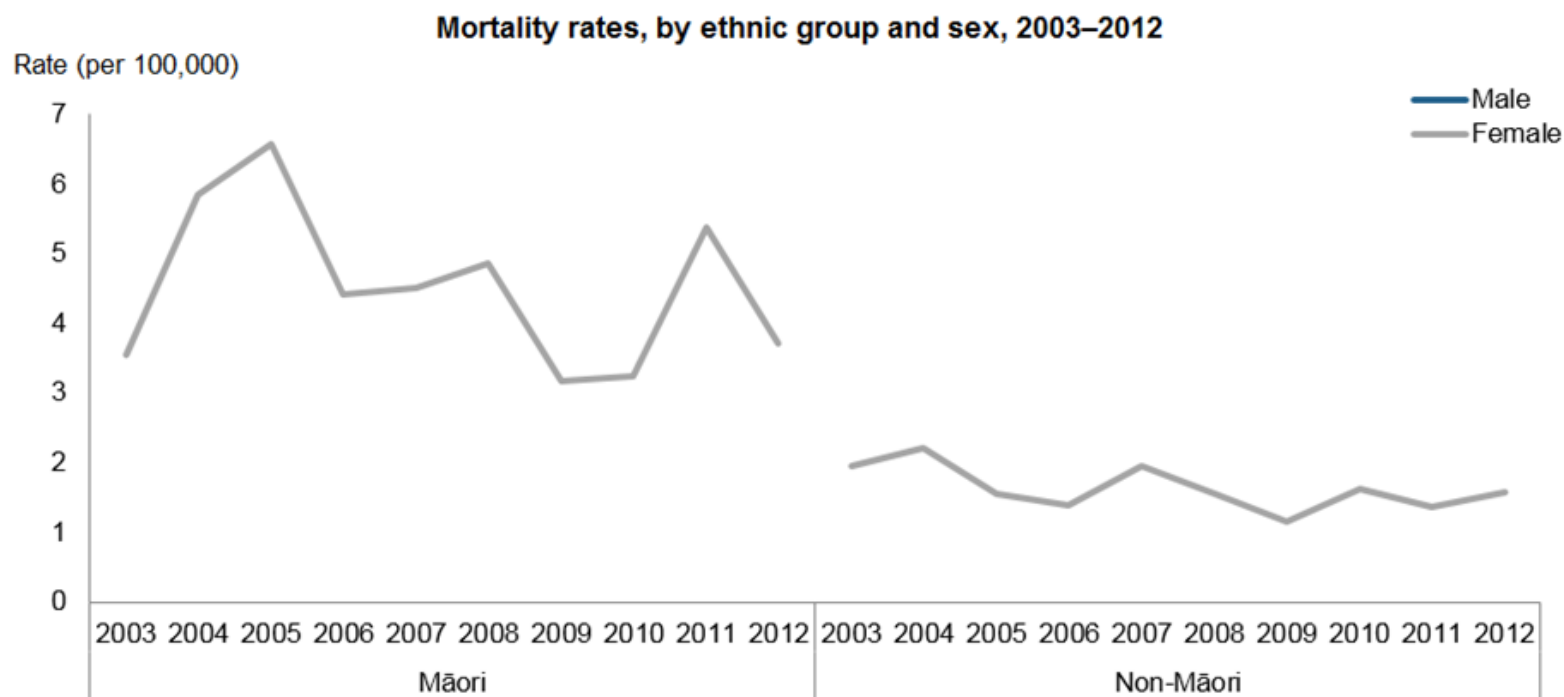
Site	% attributable to HPV
Cx	96% (95-97)
Vulva	51% (37-65)
Vagina	64% (43-82)
Penis	36% (26-47)
Anus	93% (86-97)
Oropharynx	63% (50 – 75)

Figures taken from CDC 2012 human papillomavirus-associated cancers – United States 2004 – 2008. morbidity and Mortality Weekly Report 61 (15): 258-61

NZ epidemiology

- Cx cancer rates generally dropping
 - Nearly 20% are Maori
 - Prevalence of HPV16/18 in confirmed high grade disease in Nz comparable to Australia and Europe
 - Estimates of cervical pre-cancers in NZ potentially preventable by vaccination based on 2012 data is about 2000
- Genital warts
 - Most commonly reported viral STI in NZ
 - Since 2008 (vaccination programme commenced) there has been a decline of 47% (4299 cases to 2003 cases)
- Oropharyngeal cancer (squamous cell) in males is increasing rapidly since 2005
 - Annual % change of 11.9%
 - Female increases around 2.1% per year
- Dunedin birth cohort study: 24.7% men had antibodies to any of 4 HPV types (6,11,16,18) at age 32
 - - very likely underestimate

Mortality rates for cervical cancer , by ethnic group and sex, 2003 - 2012



Genital warts case counts NZ Sexual Health and Family Planning Clinics 2006-2014

Data from ESR Annual Surveillance Report: Sexually Transmitted Infections IN NZ 2014

Genital warts case counts NZ Sexual Health and Family Planning Clinics 2006-2014

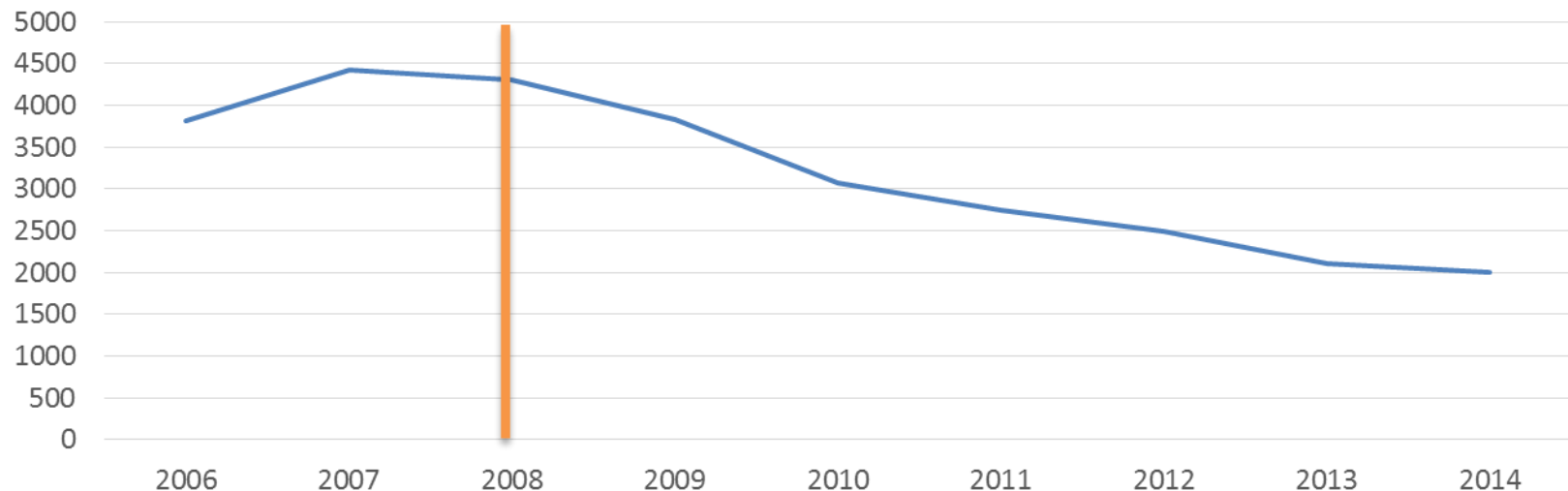


Table 1. Number of incident cancers and pre-cancers in New Zealand in 2012 potentially preventable by vaccination

	Women (n)	Men (n)	% of cases associated with HPV	% of HPV associated cases due to HPV-16,18,31,33,45,52 & 58	Cases potentially preventable by vaccination in 2012	
					Women (n)	Men (n)
Cervical cancer	166	-	100%	90%	149	-
Cervical pre-cancer	2213		100%	90%	1992	
Vulval cancer	67	-	40%	86%	23	-
Vaginal cancer	14	-	70%	88%	9	-
Penile cancer	-	15	50%	87%	-	
Anal cancer	52	20	85%	93%	23	
Cancer of the base of tongue and oropharynx	39	94	66%	94%	29	
Total	2551	129				

Based on the estimates of proportions of cancers associated with HPV, this table summarises the numbers of cases potentially preventable in 2012 by HPV9 based on cancer registry data for that year.

HPV Vaccine safety

Excellent safety profile

Summary REF: Haupt et al An overview of Quadrivalent HPV Vaccine Safety 2006 – 2015 PIDJ Sept 2015

- Extensive post marketing since 2012 – no safety signals raised
- Summary of post-market vaccine safety associations:
 - Syncope
 - Possible skin infections (but prob injection site reactions misclassified)
 - Pregnancy (contraindicated)
 - no theoretical risk ((non-live vaccine)
 - No difference in outcomes pregnant to non pregnant
- Large number of investigations for specific outcomes
 - Case reports do not equal causality Particularly autoimmune conditions
 - Extensive investigations for venous thromboembolism – do not support an association
 - MS – one study suggested an increased risk in 30 day period after vaccination, overall the data does not support this finding
 - POTS case reports. EMA review to date, no increase
 - Complex regional pain syndrome, fibromyalgia – not expected to be linked

HPV9 Vaccine



- More reactogenic than HPV4
 - Injection site reactions
 - Common systemic events (HAs, pyrexia, nausea, dizziness, fatigue) all slightly higher
 - 2.3 – 5%
 - HAs – 14.6%
- No serious adverse events
 - 2950 accidental pregnancy (out of 15000)
 - outcomes similar to placebo
 - No increase in rates of spontaneous miscarriage, birth defects, and other pregnancy outcomes to general population
 - No difference HPV9 to HPV4

Immunogenicity

HPV4

- Two dose are more immunogenic in younger ages, 9 – 15 years old
 - Young women 2 doses non-inferior to 3 doses
 - Partic. when the interval >4 months
 - HPV-18 appears to be less immunogenic than other types
- May be reduced response in immunocompromised
- Older organ transplant recipients produce suboptimal responses

Effectiveness/Impact HPV4



- Many studies documenting effectiveness and impact
 - Over 130 published studies in period Jan 2013 – June 2016
 - **Maximal reductions of around 90% for HPV infection, genital warts and cervical abnormalities** (57 studies)
- Profound reduction in genital warts (eg Australia, Denmark)
 - Elimination of genital warts may be possible
 - Mediocre coverage also leads to significant reductions
- Declines in cervical dysplasia
- Data to date supports long term effectiveness
- Younger women have the strongest evidence of protection after partial dose
- Herd immunity demonstrated for prevalence of infection, incidence of genital wart and cervical disease

Duration of protection

Table 2 Long-term studies on quadrivalent vaccine (qHPV)

Study	Study subjects	Efficacy	Seropositivity	Follow-up
P007 (Villa et al ²⁸)	Young women (age 16–23 years)	No cases of HPV 6/11/16/18-related CIN	Maintained up to 5 years	5 years
Nordic Study P015 (Nygard et al ²⁹)	Young women (age 16–23 years)	No cases of HPV 6/11/16/18-related CIN	Trend up to 9 years	8 years
Extension P018 (Iversen ³²)	Females and males (age 9–15 years)	No cases of HPV 6/11/16/18-related CIN	Maintained up to 8 years	6.8 years
Extension P019 (Luna et al ³⁵)	Adult women (age 24–45 years)	One case of HPV 6/11/16/18-related CIN	Maintained up to 6 years	6 years
P020 (Giuliano et al ³⁶)	Males (age 16–26 years)	Three cases of EGLs	–	3 years
P020 – AIN substudy (Palefsky et al ³⁷)	Males – MSM (age 16–26 years)	Five cases of AIN due to HPV 6/11/16/18	–	3 years

Abbreviations: HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; EGLs, external genital lesions; AIN, anal intraepithelial neoplasia; MSM, men who have sex with men.

Women 24 – 45 years

- High efficacy if not infected at baseline
- Overall efficacy to types 16 and 18 30.9% (11.1- 46.5)

Previously infected women

- no evidence of efficacy in pre-exposed women with vaccine types to pre-cancer (CIN3+)
(Systematic review 2014)

Miltz A, Price H, Shahmanesh M, Copas A, Gilson R. Systematic review and meta-analysis of L1-VLP-based human papillomavirus vaccine efficacy against anogenital pre-cancer in women with evidence of prior HPV exposure. PLoS ONE 2014;9:e90348.
Munoz N, Manalastas R, Jr., Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet 2009;373:1949-57.

2 dose versus 3 dose

- 6 or 12 months apart (affinity maturation principle)
- Non-inferior in girls 9-14 years
- Immunocompromised probably need 3 doses
- Will need close monitoring to ensure clinical effectiveness and durability , particularly for HPV18



Donken R, Knol MJ, Bogaards JA, van der Klis FRM, Meijer CJLM, de Melker HE. Inconclusive evidence for non-inferior immunogenicity of two- compared with three-dose HPV immunization
Dobson SRM, McNeil S, Dionne M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *Jama* 2013;309:1793-802.

April 2014: Human Papillomavirus Vaccine



World Health Organization

- SAGE concluded that immunological evidence was sufficient to conclude that a 2 dose prime-boost schedule (with a minimal interval of 6 months) was non-inferior in girls to a 3-dose schedule
- SAGE reiterated the importance of targeting HPV immunization for girls aged 9-13 years, prior to sexual debut
- Recommendations for bivalent and quadrivalent vaccine
 - 2-dose schedule with ≥ 6 month interval between doses for girls < 15 years
 - If interval between 1st and 2nd dose is < 5 months, a 3rd dose should be given at least 6 month after 1st dose
 - 3-dose schedule remains for girls > 15 years of age and immunocompromised individuals

HPV9

Pivotal study 14,215 women aged 16 – 26

- Double blind phase 2b-3 trial
- Three doses of HPV4 or HPV9 at 0,2, and 6 months
- Incidence rates of high-grade disease related to HPV 31,33,45,52 and 58 was 0.1 per 1000 person years in HPV9 and 1.6 per 100 person years in HPV4
- **HPV9 efficacy 96.7%** (80.9 – 99.8)



Joura EA, Giuliano AR, Iversen O-E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.

Delivery issues

Site

- Primarily schools
- General practice backup

Age

- Initially year 8
- Moving to year 7
- Two dose: 0,6 months (or 0,12 m)
- Catch up for all to 26 yrs of age

CATCH UP

14 year olds unvaccinated – RECALL in General Practice
?how feasible is this



Uchicago.files



Varicella Vaccines

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Sep 2016

NZ epidemiology



- Ubiquitous in NZ childhood
- Hundreds hospitalized per year
 - One tenth of cases occur in immuno-suppressed children
- 1-2 per year long term disability or death
 - Most deaths in adults
- 0.5 case per year of severe congenital varicella

References available from:



2016 Academic Review for the New Zealand National Immunisation Schedule: Varicella-zoster virus (chickenpox)

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NZ Immunisation Handbook 2014

www.health.govt.nz/publication/immunisation-handbook-2014-2nd-edn

The Australian Immunisation Handbook 10th Edition

www.immunise.health.gov.au/internet/immunise/

Varicella Vaccines

Live attenuated

Licensed in NZ:

Monovalent

- Varivax®
- Varilrix®

Combination MMRV

Priorix-Tetra®

- Given in one to two doses from 9 months of age
- Subcutaneous 0.5ml



V

MMRV
(licensed but not currently available)



Varilrix®

- Live attenuated Oka strain of varicella-zoster virus
- Mono-dose vial with a separate diluent
- Each 0.5ml reconstituted contains
 - $\geq 10^{3.3}$ plaque-forming units (PFU) attenuated varicella virus, human albumin, lactose, neomycin, polyalcohols
- Store 2-8°C
- Once reconstituted use as soon as possible
 - Hold at ambient temp not more than 90 minutes, or fridge not more than 8 hours
- 0.5ml subcutaneous
- From 9 months of age
 - 1 or 2 doses in children, 2 doses >12 years
- Minimal interval between doses: 4 weeks
- Can be given at the same time as
 - DTaP-containing vaccines, hepatitis B, Hib, MMR, Hepatitis A, pneumococcal conjugate vaccines

Effectiveness



- Single Dose
 - Approx. 80% effective
 - Against severe disease 95% plus
 - Breakthrough cases less severe
- Two dose
 - 93% -100% against severe disease
- Breakthrough varicella in vaccinated people
 - Usually attenuated
 - Severity does not increase with time post vaccination
- Immunocompromised
 - Effectiveness unclear
 - Disease severity reduced
 - Mild immunosuppression still get seroconversion



Duration of protection

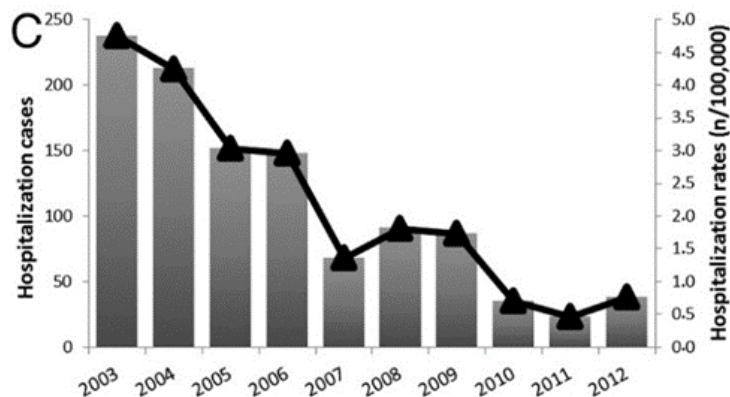
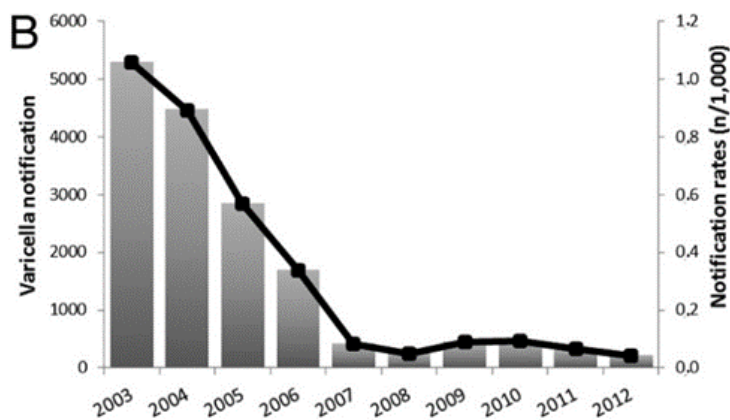
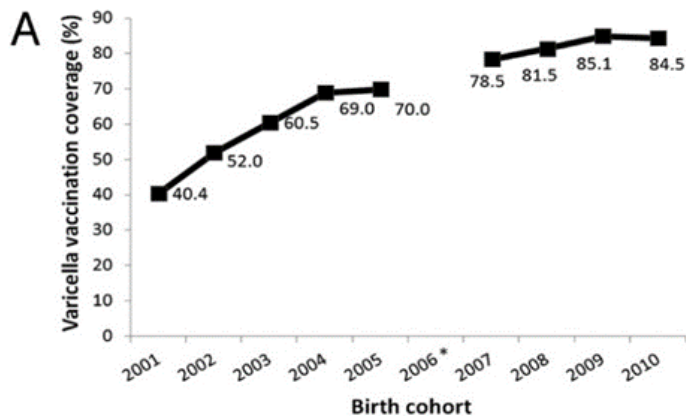
- One dose
 - Not yet defined, but breakthrough disease does not become more severe with time
 - US study VE declined from 88.8% to 81.8% after >10 years
 - Some effect from circulating wild disease causing boosting
 - Therefore reductions in circulating disease may reduce duration of protection
- Two-dose probably long lasting
 - NB second dose also acts as a booster (unlike measles vaccination)
 - No breakthrough after 14 years post two doses
 - Many countries introduce a few years after starting one dose
 - Universal 2 dose in US since 2006

Impact of varicella vaccination programmes

- Significant reductions in severity of disease, hospitalisations and circulation of varicella in all regions that have introduced varicella
 - US (one dose in 1995, two doses in 2007)
 - 90-95% reduction in varicella in 5-19 yr olds
 - No evidence of shift in burden to older age groups
 - 10 fold reduction in varicella hospitalisations
 - 99% decline in mortality for <20yrs
 - Declines in all age groups, including infants too young to be vaccinated
 - Similar impacts in Germany (1 dose 2004, 2 dose 2007) ,Saudi Arabia (2 dose 1998) Canada (1 dose 2000-2007, six provinces dose 2), Italy and Spain region by region,
 - Australia: Single dose 2005, second dose as MMRV 2013

Baxter R, Tran TN, Ray P, et al. Impact of vaccination on the epidemiology of varicella: 1995-2009. *Pediatrics*. 2014;134(1):24-30.

Leung J, Bialek SR, Marin M. Trends in varicella mortality in the United States: Data from vital statistics and the national surveillance system. *Human Vaccines and Immunotherapeutics*. 2015;11(3):662-8.



(A) Varicella vaccination coverage by birth cohort in Sicily (*birth cohort data lacking); (B) Notifications for varicella in Sicily, 2003-2012; (C) Hospitalisations with varicella diagnosis in Sicily 2003-2012. Reproduced with permission (Amodio et al).

Amodio E, Tramuto F, Cracchiolo M, et al. The impact of ten years of infant universal Varicella vaccination in Sicily, Italy (2003-2012). Hum Vaccin Immunother. 2015;11(1):236-9.

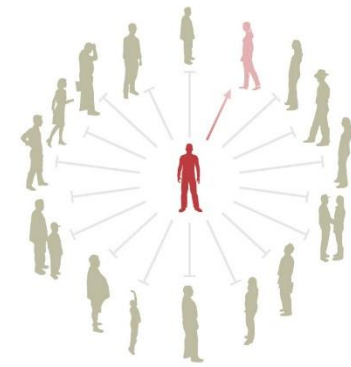
Impact of varicella vaccination programmes (2)

- Where varicella still in circulation , significant reduction in disease in younger age groups, disease incidence can be pushed to the older children, adolescents
 - Therefore vaccination of non-immune adolescents is warranted
 - Many countries have funded adolescent catch-up

Baxter R, Tran TN, Ray P, et al. Impact of vaccination on the epidemiology of varicella: 1995-2009. *Pediatrics*. 2014;134(1):24-30.

Leung J, Bialek SR, Marin M. Trends in varicella mortality in the United States: Data from vital statistics and the national surveillance system. *Human Vaccines and Immunotherapeutics*. 2015;11(3):662-8.

Herd immunity



<http://graphics8.nytimes.com/newsgraphics/2015/02/02/measles-facts/01f7c7331715b51a58bc4380fd8031c56bcd27a1/herd-3-artboard-10.jpg>

Where universal programmes have been implemented significant declines in cases and hospitalisations have been seen, including those not vaccinated – infants and immunocompromised

For example: Canada concluded that decreases in varicella circulation contribute significantly to decliners in varicella-related hospitalisations for young infants and adults aged 20 -39 yrs

AEFIs

- Generally mild and self limiting
 - Fever: Possible 5-12 days post vaccination
 - 1-3% localized rash
 - 3-5% generalized varicella-like rash
 - 5-26 days post vaccination
 - Usually 2-5 lesions, can be maculopapular
- ? Transmission of vaccine virus to others:
 - Possible but extremely rare
 - Err on the side of caution
 - If there is a post-immunisation rash isolate from any immunosuppressed contacts, cover rash
- Noted but not necessarily causally linked
 - Encephalitis, ataxia, thrombocytopenia, anaphylaxis <0.01%

Safety profile



Immunocompetent

- 2008 review AEFI 3.4/100 000 doses (based on 55.7 million doses during 1995 – 2005 worldwide)
- Post-market surveillance USA serious adverse events <4/100 000
- Most frequently reported reactions mild and primarily injection site reactions (systematic review SAGE)
- Site pain, swelling, redness : 28%
- Local or generalized rash fairly frequent
- ITP with adolescent vaccination, rare but possible – all mild and acute
- Anaphylaxis reported but very rare
- No increased risk of febrile seizures with monovalent varicella vaccine alone at 11 months of age
- No increase risk of cerebellar ataxia, encephalitis or ischaemic stroke



Safety profile (2)

Immunocompromised

- Higher risk in children with cell-mediated immunity deficiencies
- Can use cautiously in children closely monitored oncology situations, treatments regimes for juvenile arthritis
- Undiagnosed immunocompromised – rash, vaccine strain viral reactivation and subsequent infections dissemination, pneumonitis, meningitis, hepatitis, fatal outcomes

MMR-V

- Increase in febrile convulsions in dose one if given 12 – 23 months: excess cases
 - MMR + V (separate injections) = 3-4/100 000
 - MMRV = 7-9/100 000 (excess of 4.2/100 000) ref 34
 - Peak age 16-18 months and incidence 5 – 12 days post vaccination
 - Overall one additional febrile seizure per every 2,300 doses
 - Incidence of seizures highest in 16 -18 months
- Use of MMRV doubles the risk of seizures at 12 -15 months and 16-23 months
- No increase in febrile convulsions when used as dose 2

NB delaying MMR dose one until 16 months or older increases relative risk of seizure by 3 times compared with on time vaccination

Post exposure prophylaxis



A single dose is highly effective when administered within 3-5 days of exposure (79 – 100%)

Break through cases tend to be more mild

World Health Organization. Varicella and herpes zoster vaccines: WHO position paper, June 2014. Wkly Epidemiol Rec. 2014;89(25):265-87.

Macartney K, Heywood A, McIntyre P. Vaccines for post-exposure prophylaxis against varicella (chickenpox) in children and adults. Cochrane Database Syst Rev. 2014;6:CD001833.

Marin M. Updated recommendations for use of VariZIG - United States, 2013. American Journal of Transplantation. 2013;13(10):2765-7.

Contraindications

- General Vaccine contraindications
 - Anaphylaxis to vaccine components
 - Acutely unwell
- Immunocompromised
 - Primary or acquired T-cell deficiency states
 - High dose steroids for >2 weeks
 - Known anaphylaxis to neomycin
 - Active untreated Tb
 - In pregnancy
- Relative contraindications
 - Children on salicylates (association with Reye syndrome)
- Precautions
 - On the advice of a specialist:
 - 2 years post bone marrow transplantation
 - 6 months post chemotherapy
 - HIV-positive with mild or mod immunosuppression
- Breast feeding – NO concerns, NOT a contraindication



Contraindications

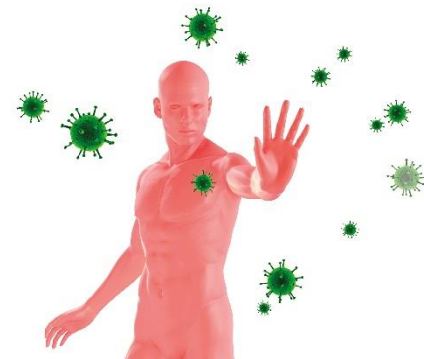
- **Pregnancy**

- Pregnancy register data for 17 years (928 reports when inadvertently given)
 - No congenital varicella syndrome
 - No increased birth defects
 - Register closed in 2013



- **Immunocompromised**

- But limited capacity for virulence or replication:
- Mild immunocompromised benefits probably outweigh risks eg HIV on treatment, one year post organ transplant recipients on maintenance immunosuppression
- Closely monitored oncology patients, on Rx for juvenile arthritis
- CAUTION, TAKE ADVICE
- Can treat with antivirals



Refer page 502 NZ Immunisation Handbook 2014



Herpes zoster

- Zoster can occur post vaccination but lower rates
 - 48/100 000 in vaccinated versus 230/10 000 in unvaccinated
 - US study vaccinated children had 79% lower incidence of zoster
- If zoster is prevented by exogenous boosting (ie exposure to circulating varicella)
 - Theoretically stopping varicella circulating could increase the incidence of zoster in older groups
 - BUT - No definite increase has been demonstrated in countries that have introduced varicella vaccination. No definitive increase has been seen overall in the US or Australia

Weinmann S, Chun C, Schmid DS, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. *J Infect Dis.* 2013;208(11):1859-68.

Hales CM, Harpaz R, Joesoef MR, et al. Examination of links between herpes zoster incidence and childhood varicella vaccination. *Ann Intern Med.* 2013;159(11):739-45.

Heywood AE, Wang H, Macartney KK, et al. Varicella and herpes zoster hospitalizations before and after implementation of one-dose varicella vaccination in Australia: an ecological study. *Bull World Health Organ.* 2014;92(8):593-604.

Delivery

- Private market
 - One or two doses from 9 months of age
 - 13 years plus: Two doses
- From July 2017
 - **Single dose at 15 months**
 - Four injections
 - Alongside Hib, PCV10 and MMR
 - **Catch up in General Practice for 11 year olds with no prior history of varicella or vaccination**



Evidence for effective multiple injections at one visits is around the **CONFIDENCE OF THE PROVIDER**, more than the parent



<https://nz.pinterest.com/pin/420382946438105287/>



<http://www.mightynurse.com/wp-content/uploads/2012/03/bold-confident-mighty-nurse.png>

Adolescents and adults

- recommended not funded

ANYONE with no history of varicella and/or negative serology

PARTICULARY

- Born and resided in tropical countries, with no history of varicella infection
- Those who live or work in environments where transmission is likely eg ECC, institutional settings, HCWs, military
- Non-pregnant of childbearing age
- International travelers
- Post exposure

Other National schedules

Variable

- 1 or 2 doses
 - Many countries start with one dose
 - Add in a second dose up to a decade later eg US, Canada
- Concomitant use with MMR
 - Usually with second dose
- ?role of catch up campaigns for adolescents and adults
 - unclear
- Surveillance variable
 - Notifiable in some countries eg Scotland, Northern Ireland
 - Not notifiable in England and Wales
 - Not currently notifiable in NZ



- I want to offer my child protection earlier than 15 months
 - Private market from 12 months
- I don't wish to give 4 injections at once
 - Are they sure?
 - Concerns re toddler memories and multiple visits with injections
 - If sure: Given MMR and Varicella first
 - Hib and PCV can be given AT ANY TIME afterwards, no gap needed



- Why doesn't the national schedule offer a two dose regime
 - As per earlier data
- I wish to use the MMRV, rather than separate injections
 - Not funded
 - Increased risk of fever and febrile convulsions



- How do I protect my immunosuppressed individual who has never had chicken pox
 - Ring protection
- How do I know if I need the vaccine , do I need a blood test?
 - History varicella is acceptable. Do not need serology
 - No clear history :70 -90% will still be immune, can chose serology or vaccination.
 - Serology availability varies from lab to lab, ck costs

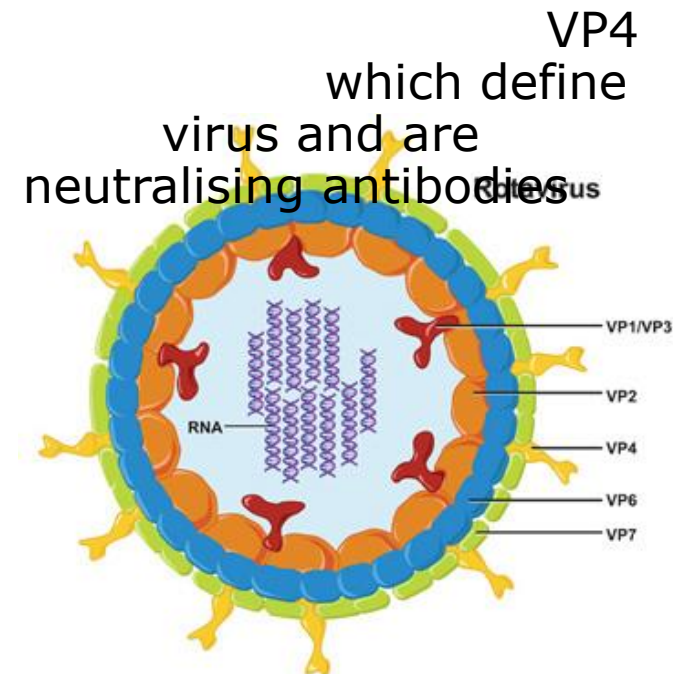


Rotavirus vaccine: - brand shift

Ref: 2012 Antigen Review for the New Zealand National Immunisation Schedule: Rotavirus. IMAC, University of Auckland

Rotavirus: the virus

- Wheel shaped virus (*rota* is Latin for wheel) from the family *Reoviridae*
- Triple layer is made up of six structural proteins:
 1. Inner most layer made up of VP2 structural proteins enclosing the VP1 and VP3
 2. Middle shell is made up of VP6
 3. Outermost layer contains (P protein) and VP7 (G protein) which define the serotype of the virus and are targets for neutralising antibodies



Rotavirus Disease (1)

- 1 in 5 children will have sought medical advice for infection by 5yrs of age
- 1 in 43 children will have been admitted for rotavirus infection
- Spread by fecal-oral route
- Responsible for up to 50% of gastroenteritis in NZ



History.....Rotavirus vaccines

- The first rotavirus vaccine (Rotashield) used in the 1990s in the USA was shown to have an association with intussusception (and was withdrawn)
- Very large clinical trials prior to licensure of current rotavirus vaccines showed no increased risk
- Post licensure some increased risk up to 3 wks post dose one has been shown
- It is uncertain whether rotavirus vaccine administration affects the overall incidence of intussusception, the condition remains rare and this risk is outweighed by the benefits of rotavirus vaccination in preventing rotavirus infections

Vaccines

Rotarix (RV1)

- Live attenuated
- Human rotavirus strain
- P1A[8]G1

- 2 dose
- oral

Rotateq (RV5)

- Live attenuated
 - Pentavalent human-bovine assortment
 - G types 1-4(VP7) and P[8] (VP4
-
- oral
 - 3 dose
 - 3rd dose no later than 8 months of age

Effectiveness against any rotavirus disease

Similar for both vaccines

- 44-51% low income settings
- 76-86% middle income settings
- 80-85% higher income settings
- More effective against severe disease
- Some cross protection seen against other strains

Table from Cochrane review: percentage of severe rotavirus and all cause diarrhoea cases prevented in children by RV1 and RV5, compared to placebo in low mortality rate countries

Vaccine	Percentage of cases prevented	Risk ratio (95% confidence interval)	Number of participants (number of trials)	Quality of evidence
Severe rotavirus diarrhoea: infants aged under one year				
RV1	86	0.14 (0.07–0.26)	40,631 (6)	high
RV5	87	0.13 (0.04–0.45)	2344 (3)	moderate
Severe rotavirus diarrhoea: children aged under two years				
RV1	85	0.15 (0.12–0.2)	32,854 (8)	high
RV5	82	0.18 (0.07–0.5)	3190 (3)	moderate
Severe all-cause diarrhoea: infants aged under one year				
RV1	40	0.60 (0.5–0.72)	17,867 (1)	moderate
RV5	72	0.28 (0.16–0.48)	1029 (1)	low
Severe all-cause diarrhoea: children aged under two years				
RV1	37	0.63 (0.56–0.71)	39,091 (2)	moderate
RV5	96	0.04 (0.00–0.70)	5916 (1)	low

Source: Adapted from: Soares-Weiser K, MacLehose H, Bergman H, Ben-Aharon I, et al. 2012. Vaccines for preventing rotavirus diarrhoea: Vaccines in use. *Cochrane Database of Systematic Reviews* (11). 10.1002/14651858.CD008521.pub3 (accessed 12 August 2013).

Expected responses and AEFI

Mild and Common

- Very mild diarrhoea or smelly faeces for a few days
- Vomiting
- Windy ++
- Pyrexia

Rare and Severe

- Intussusception

Contraindications

- Moderate to severe illness (temp over 38⁰C)
- History of a severe allergic reaction after a previous dose or to a vaccine component.
- Should not be given to:
 - infants with acute moderate or severe gastroenteritis until the condition improves.
 - infants with a history of intussusception or an uncorrected congenital malformation of the gastrointestinal tract that would predispose the infant to intussusception
 - infants with severe combined immune-deficiency syndrome.

Delivery

- First dose 6 weeks, second dose 3 months
 - MUST be complete by 24 weeks of age
- Administer first
 - Sucrose content reduces pain for injectable vaccines
- Handwashing
- Interchangeability
 - No data, but expected to be fine
 - If started with Rotateq, can complete with Rotarix
 - Must be within the 24 weeks

Preterm Infants

- Recommended that preterm infants are vaccinated as they leave hospital
- If discharge is likely to be > 15 weeks of age then it is considered acceptable to give the vaccine whilst the infant is still in hospital
- Standard universal precautions should be maintained to ensure low risk for transmission of vaccine viruses



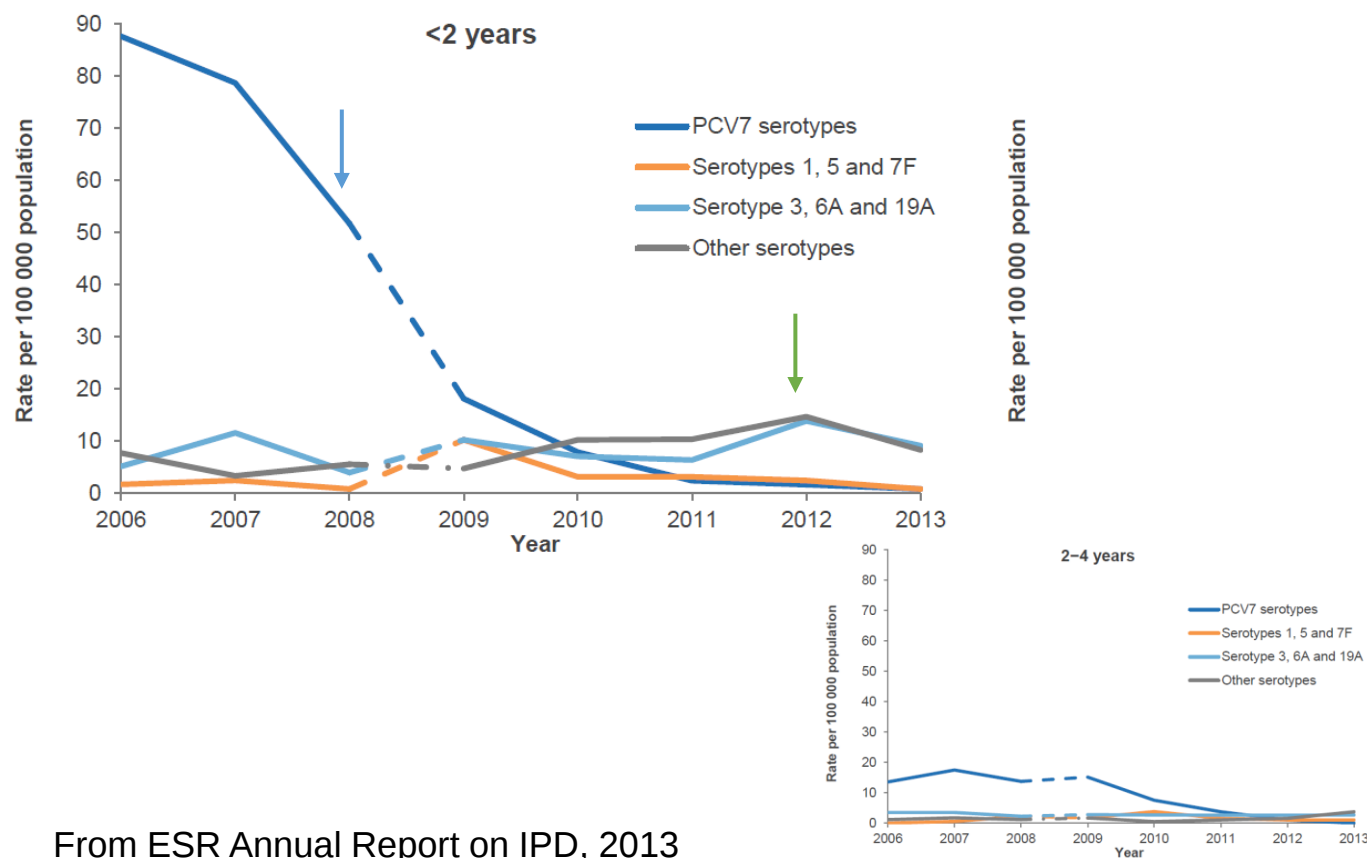


Pneumococcal Conjugates: - brand shift

Pneumococcal Vaccines in NZ

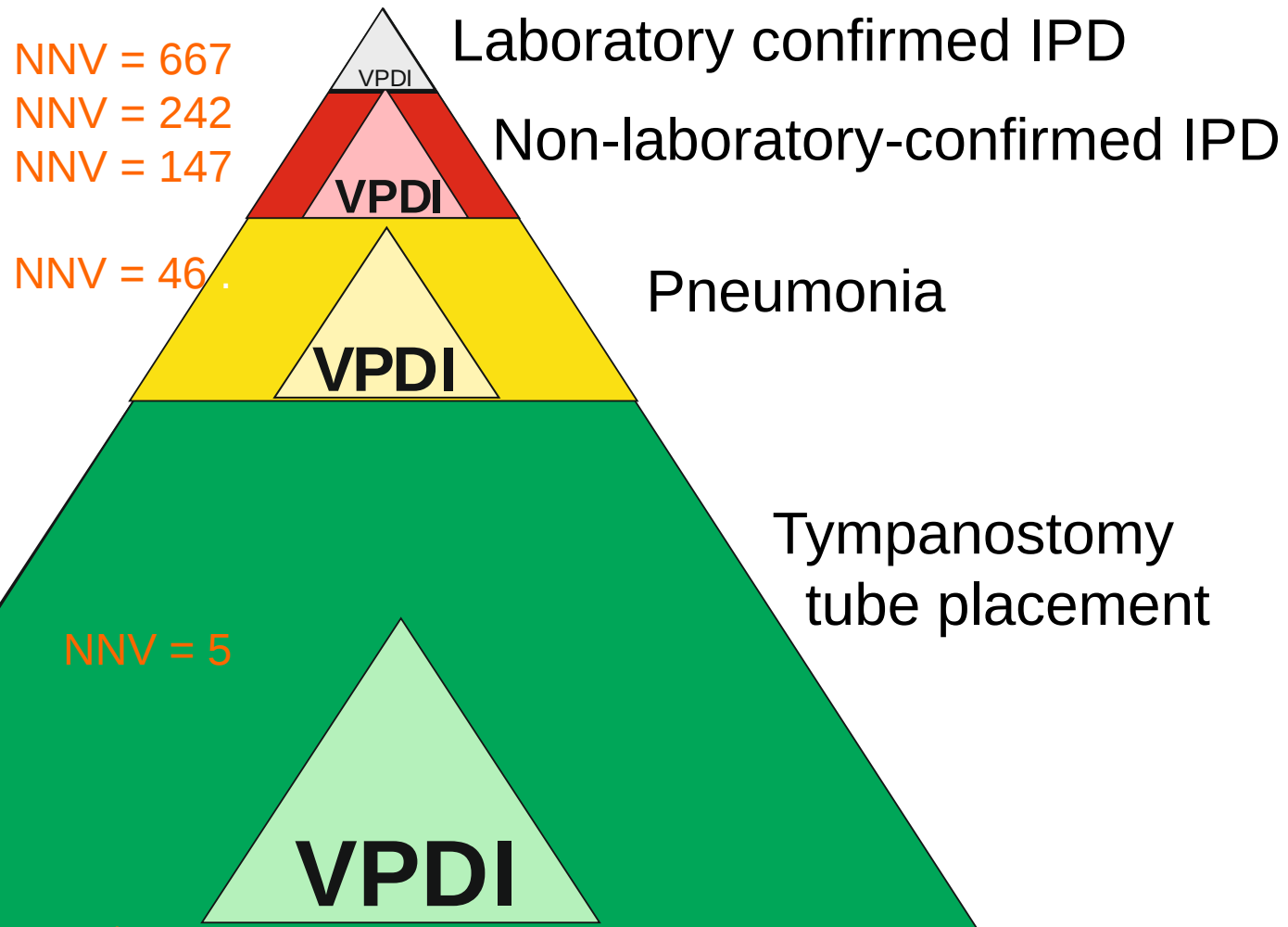
- Prevenar and Pneumovax 23 introduced 2006 for high risk groups only
- Prevenar on the national schedule 2008
- Replaced by Synflorix (PCV10) July 2011
 - PCV13 and PPV23 remained for high risk children
- Replaced by Prevenar13 July 2014

Use of pneumococcal vaccine has impacted on invasive disease



From ESR Annual Report on IPD, 2013

Disease burden and vaccine-preventable disease incidence (VPDI) in children vaccinated in infancy (courtesy Dr Bernard Hoet, GSK)



NNV = 4 to prevent any outcome

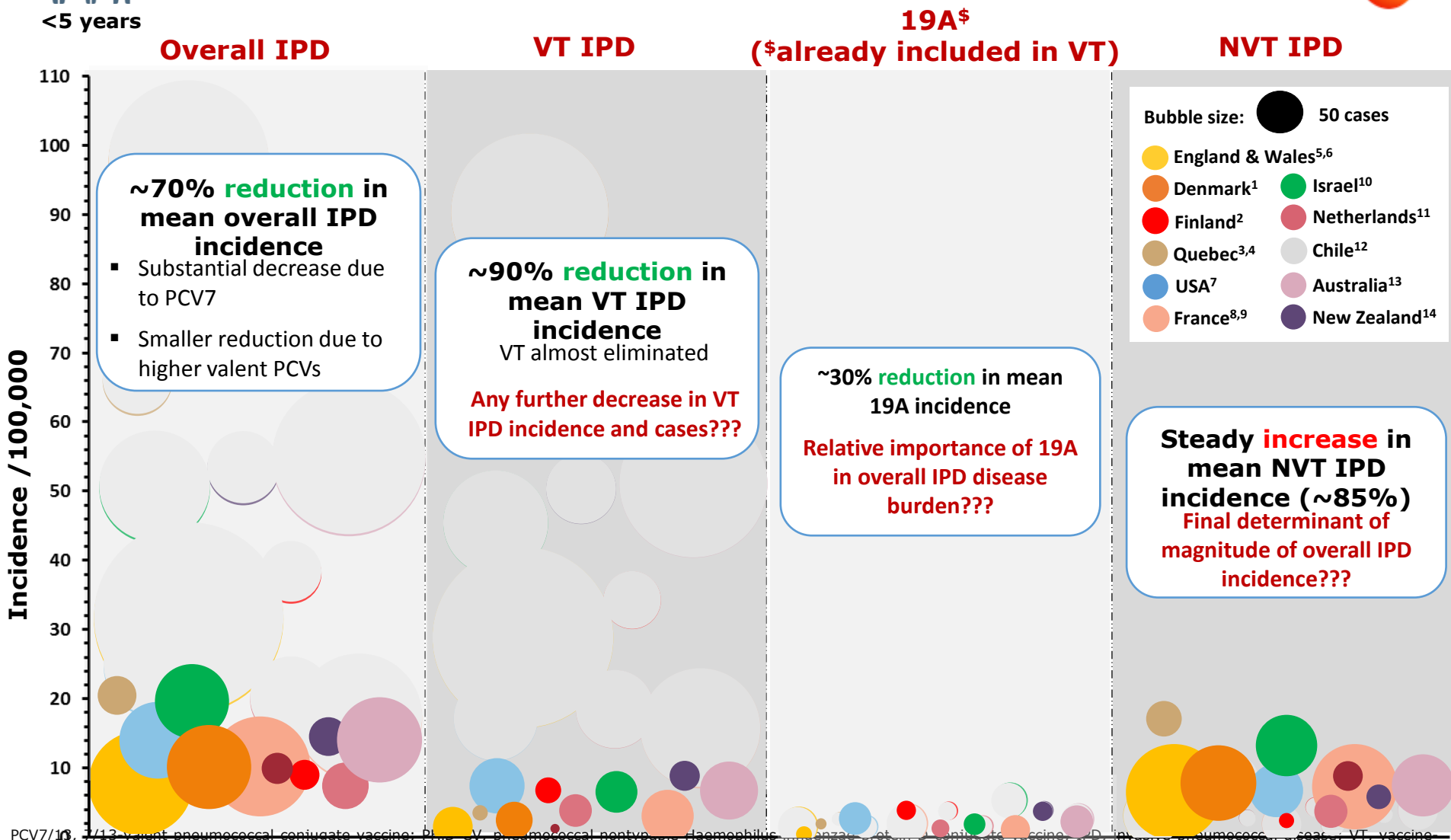
Graphics based on true incidences

Adapted from Palmu et al, ESPID 2014, Dublin, Ireland



<5 years

Summary: unpublished data courtesy Dr Bernard Hoet

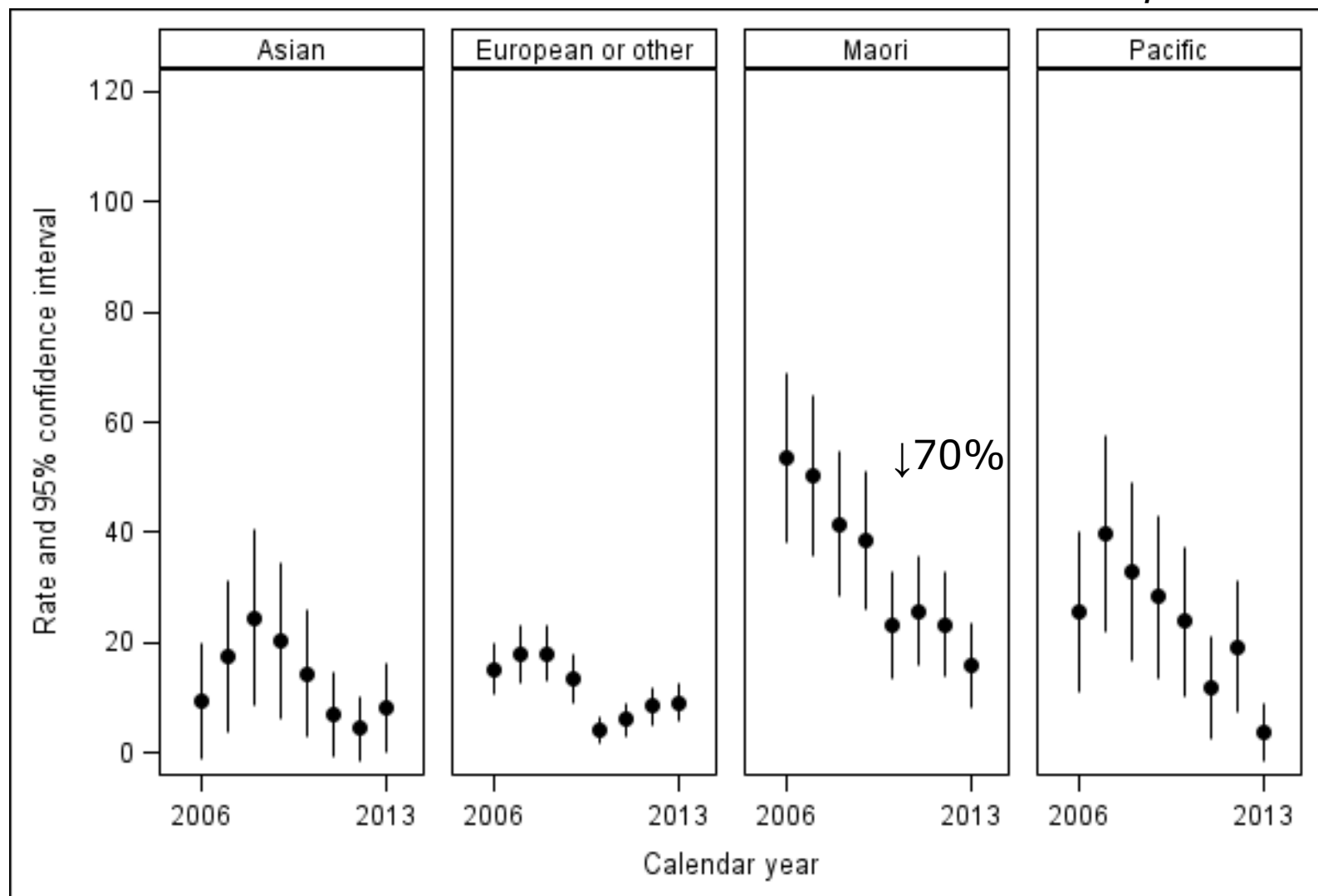


PCV7/10, 7/13 valent pneumococcal conjugate vaccine; PNV, pneumococcal non-typeable Haemophilus influenzae, rotavirus conjugate vaccine, 2D, inactivated pneumococcal vaccine; VT, vaccine preventable serotypes; NVT, non-vaccine preventable serotypes.

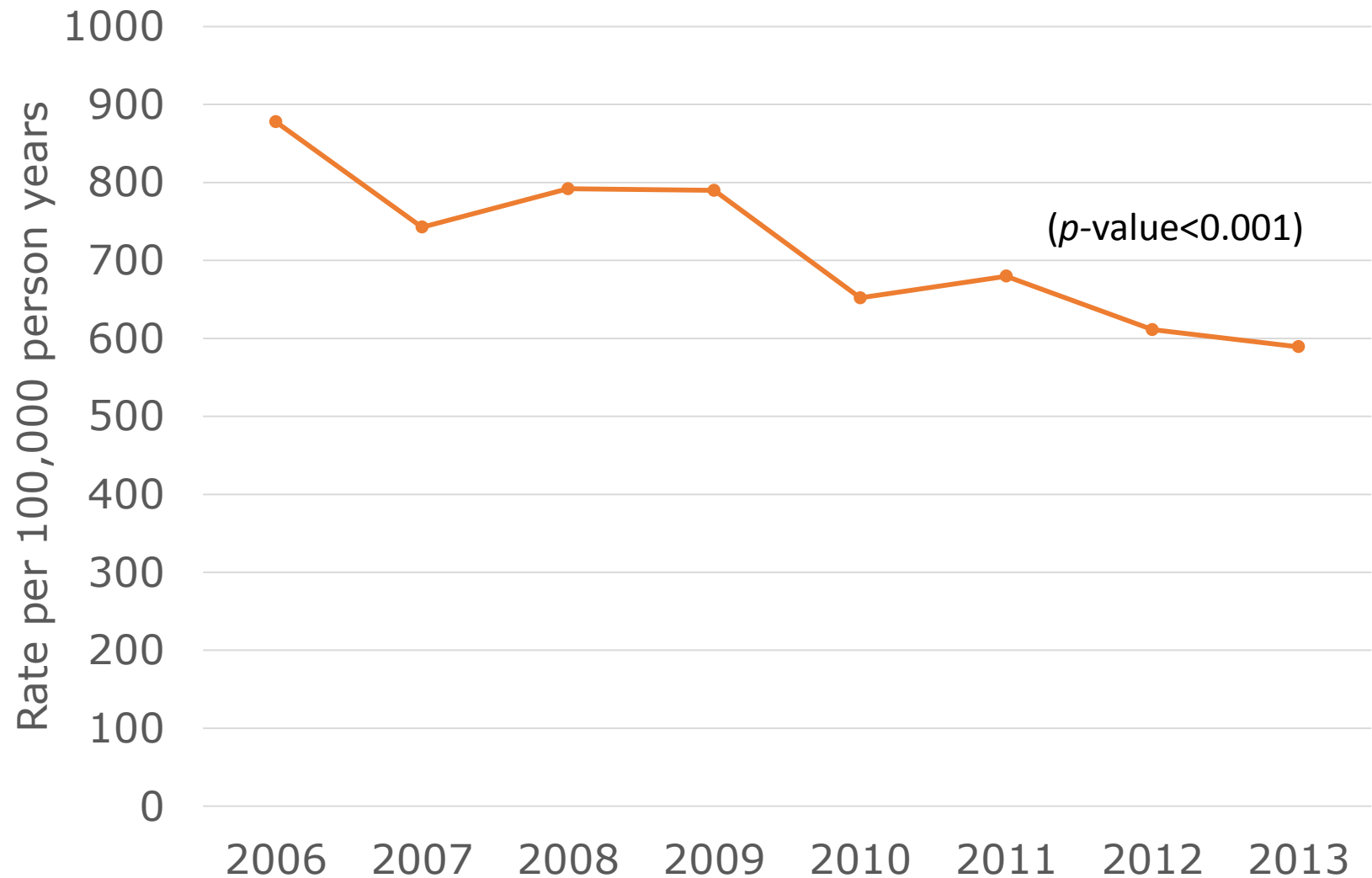
1. Vaccine Nordic Meeting 2016, <http://nvm2016.is/sites/default/files/zitte%20barella.pdf> [accessed Aug 2016] and <http://www.statbank.dk/10021> (for population data)[Accessed Aug 2016]; 2. THL Finland. <https://www.thl.fi/en/web/thlfi-en/topics/information-packages/incidence-of-invasive-pneumococcal-disease-in-finland> [accessed Aug 2016]; 3. INSPQ report, https://www.inspq.qc.ca/pdf/publications/2081_surveillance_pneumocoque.pdf [accessed Aug 2016]; 4. De Wals P, et al. *Vaccine* 2014;32:1501-1506; 5. Waight PA, et al. *Lancet Infect Dis* 2015; 15: 535-43; 6. Miller E, et al. *Lancet Infect Dis* 2011;11:760-68; 7. Centre for Disease Control and Prevention, Active Bacterial Core Surveillance 1998-2014, <http://www.cdc.gov/abcs/reports-findings/surv-reports.html> [accessed Aug 2016]; 8. Lepoutre A, et al. *Vaccine* 2015;33:359-366; 9. CNRP 2013 and 2014 report, <http://cnr-pneumo.com/> [accessed Aug 2016]; 10. Ben Shimol S, et al. *Vaccine* 2014;32:3452-3459; 12. Knol MJ, et al. *Emerg Infect Dis* 2015;21(11):2040-4; 12. Chile Instituto de Salud Pública, July 2015, <http://www.ispch.cl/sites/default/files/Bolet%C3%ADn%20de%20Vigilancia%20de%20Laboratorio%20de%20Streptococcus%20pneumoniae.pdf> [accessed Aug 2016]; 13. NNDSS IPD Quarterly reports 2014-2016, <http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-ipd-reports.htm> [accessed Aug 2016]; 14. ESR IPD reports 2013-2015 <https://surv.esr.cri.nz/surveillance/IPD.php> [accessed Aug 2016].

Ethnic differences in IPD hospitalisations in <6 year olds decreased between 2006 to 2013

$p = < 0.045$



Hospitalisations for all-cause pneumonia among children less than 6 years of age



Current Conjugate Pneumococcal Vaccines



PCV10 (Synflorix)

- 1,4,5,6B,7F,9V,14,18C,19F,23F
- Conjugate
 - Protein D from non-typeable H. influenza
 - Tetanus toxoid
 - Diphtheria toxoid (CRM₁₉₇)
- Theoretical advantage in Protein D conjugate may offer better protection against OM
 - Not proven
- International evidence shows some cross-protection to 19A

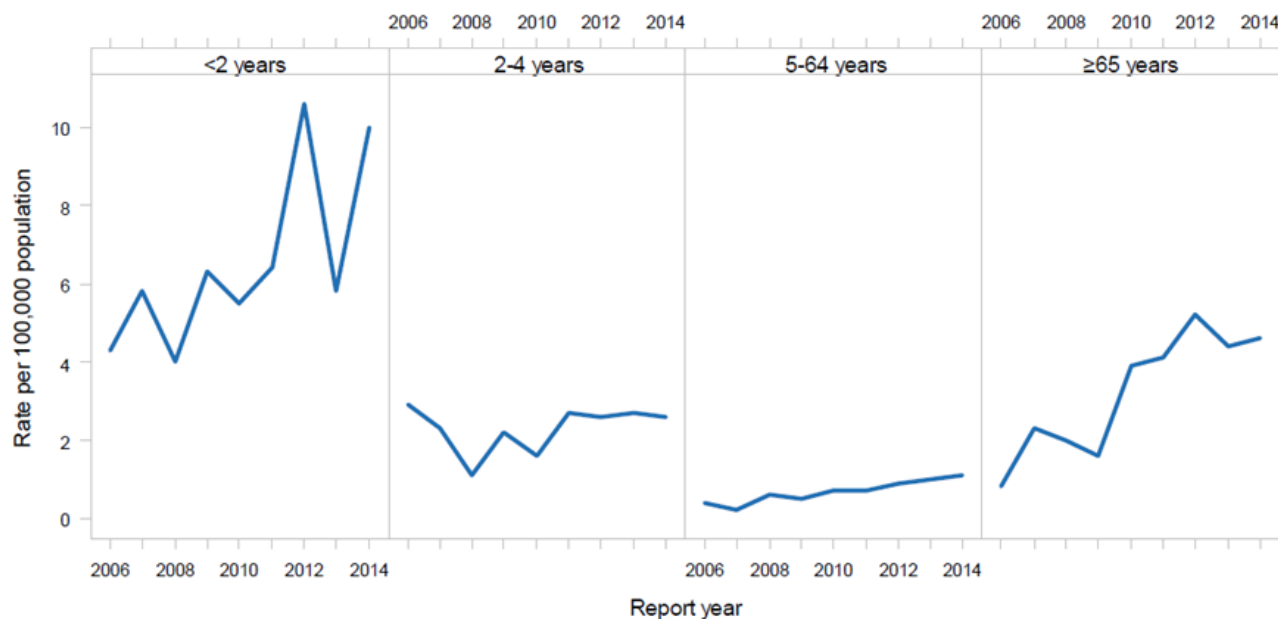
PCV13 (Prevenar13)

- Also includes 2, 3, 19A
- Conjugate:
 - Diphtheria toxoid (CRM₁₉₇)

Type 19A: difficult to predict

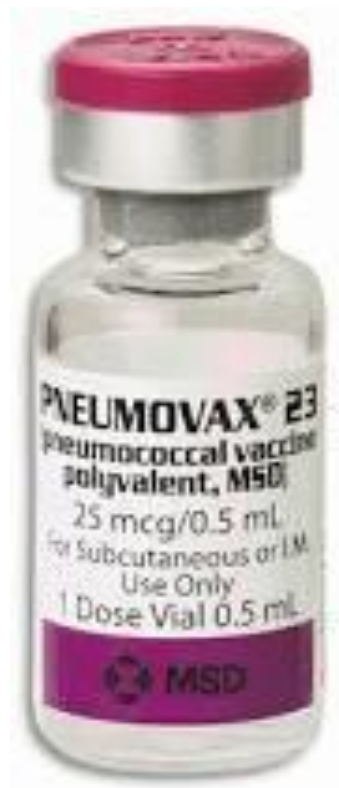
IPD associated with serotype 19A has fluctuated in the periods 2001 – 2015. The year with the highest rate in children under 2 years of age per 100,000 was 2012. Rates dropped in 2013 then climbed again in 2014.

Among older adults the rate has generally climbed each year since 2008 to peak in 2015.



Note: Data presented from 2009 onwards is based on IPD notifications and data prior to 2009 is from ESR's national laboratory-based surveillance of IPD.

?and the role of PPV23 (Pneumovax23)



Vaccines against encapsulated bacteria

Hib, pneumococcal, meningococcal

Polysaccharides

- 1970s technology
- Don't work effectively in children <2 years
- Primarily B cell response only:
 - low affinity Ab production only
- No immune memory generated
 - No induction of T cells
 - Cannot boost immunity
 - Hyporesponsiveness with repeated doses
 - No effect on carriage

Pneumovax23

Mencevax ACWY, Menomune ACYW135

Conjugates

- Newer technology
- Effective in children < 2 years
- Immune memory and maturation due to induction of T-cells
 - High affinity Abs
 - Potential to boost (secondary response)
 - Effective in carriage reduction

HiB

Synflorix, Prevenar13

NeisVac, Meningitec, Menactra

High risk groups for pneumococcal disease

- PCV13 followed by PPV23

FUNDED

HIV, chemotherapy pre or post splenectomy, functional asplenia, pre or post transplant or haemopoietic stem cell transplant, renal dialysis, complement deficiency, cochlear implants, primary immunodeficiency

Other groups being considered.....

Delivery issues

- In practice the vaccines are interchangeable
- If course started with one brand, ok to change to other
- For high risk groups
 - PCV13 followed by PPV23



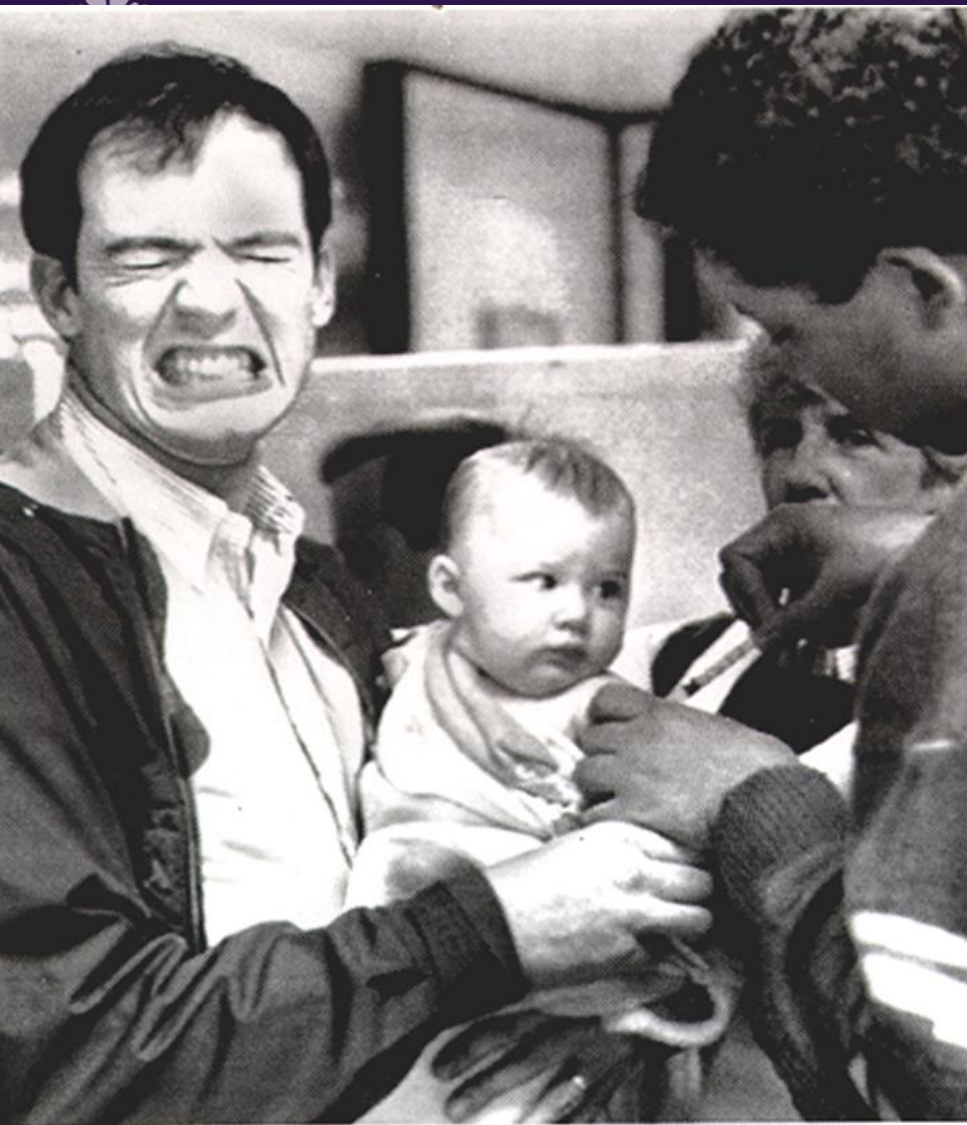
?role of Pneumococcal vaccines in the elderly

PPV23 – some effectiveness against IPD, not against pneumonia

PCV13

- CAPITA study (Bronten et al March 25 2015 NEJM)
- in Dutch population
 - 75% (41 – 92) effective against vaccine-strain invasive IPD
 - 45% (14 – 63) effective against vaccine-strain types community-acquired pneumonia
 - Efficacy lasted up to 4 years
- Adults >65yrs: 13% of all pneumonia was vaccine-strain

The role of Pneumococcal vaccines in elderly is unclear
There is probably a role for HIGH RISK groups eg COPD
- **Personally I recommend PCV13 followed by PPV23**



Mitigation of Pain or Distress on Vaccination

Helping your baby during vaccinations

A New Zealand parent/whanau guide: Babies up to 1 year old

Vaccine injections can sometimes be distressing for babies and stressful for parents, but you can really make a difference. For your baby's next vaccination, you can talk with your nurse about pain management options which might work for you and your baby:

1. If your baby is breastfed try to time your appointment so you can breastfeed.
2. If your baby uses a dummy or has a comforter bring it along with you.
3. Read the pain management ideas below and combine these strategies to improve pain relief

What you can give (and what not to give)



The RotaTeq vaccine (sucrose solution)

- Your health professional can give the RotaTeq vaccine to your baby to drink right before the injections. The sucrose in this vaccine can reduce injection pain in babies. Sucrose solutions (sugar water) are proven to reduce pain during vaccinations for about 5- 10 minutes. This is only used for medical procedures.

Avoid paracetamol (Pamoltm), ibuprofen (Nurofentm, Fenpaedtm), ice and cold spray before injection – these have not been proven to reduce injection pain in babies and the medicines may affect the immune response. After injection paracetamol or ibuprofen may be used to relieve distressing pain.

What you can do



Breastfeed

- Start breastfeeding your baby before injection and continue during and after injections. Uncover your baby's legs before you begin your breastfeeding
- If your baby cannot be breastfed, offer a dummy (pacifier) starting before the injections and continue during and after the injection



Hold upright

- If you are not breastfeeding hold your baby upright and close during injections – in a hug or on your lap. This feels good and helps your baby stay still.
- Avoid holding your baby too tightly – this can increase pain and distress

How you can act



Breathe deeply

- Stay calm and use your normal speaking voice. This helps your baby stay calm –babies look to their parents for how to act and feel.
- If you are nervous, take a few slow, deep breaths to calm yourself before and during the injections – breathe so your stomach expands, not your chest. You can do this while holding your baby.

Distract

- If you are not breastfeeding you can help keep your baby's attention away from the injection by gently distracting them
- Distractions can include cuddling, singing, talking to them, and giving them a dummy to suck. After the injections you can gently distract with rocking, cuddling, swaddling (wrapping) and shushing (saying "SHHH SHHHH").

These are scientifically proven ways of reducing pain or distress in babies during injections. Think about what worked and plan ahead to make the next vaccination comfortable. These techniques can also be useful for blood tests and heel pricks.

Helping your child during vaccinations

A New Zealand parent/whanau guide: Children over 1 year old

Vaccine injections can sometimes be stressful for children and parents, but you can really make a difference.

For your child's next vaccine injection, talk with your health care provider about which options may work for you:

1. Bring an age-appropriate toy to help distract your child.

2. If your child is 4 years or older, prepare them ahead of time (on the day or the day before) – this helps them cope.

With children over 4 years old talk about:

- What is going to happen : "You will get vaccinations in your arms"
- What it might feel like : "There may be a pinch or pressure for a few seconds"
- What you will do to help it feel more comfortable: "We are going to do some things so it doesn't bother you"
- What your child can do: "You can help by choosing a toy to bring"
- Do not tell children "it won't hurt" because this doesn't help ; instead tell them what you will do to make it more comfortable

3. One choice is EMLA[™] topical anaesthetic cream to numb the skin – you can buy this medicine at a pharmacy without a prescription for about \$20. If you don't choose this option you can still use the other strategies.

4. Read the pain management tips below, you can combine any of these strategies to improve pain relief.

What you can do



Sit upright or hold

- Have your child sit up or hold your child on your lap in a hug during the injection
- Avoid holding your child too tightly – this can increase pain and distress

Vibration on the skin

- Vibration on your child's arm or leg near the injection site right before and during injections can create 'white noise'. Some clinics may have a vibration device which works in this way.
- Do not rub the injection site afterwards.

How you can act



Breathe deeply

- Stay calm, use your normal speaking voice. This helps your child stay calm – children look to their parents/whanau for how to act and feel
- If you are nervous, take a few slow, deep breaths to calm yourself before and during injection – breathe so your stomach expands, not your chest. Gently distract your child before the injection, and continue during and after injection

Distract

- Distractions include music, singing, videos, books, bubbles, windmills, toys, phone or tablets
- Acknowledge your child's pain, but do not focus on it – this can increase pain and distress
- Direct your child to take slow deep breaths. Use bubbles/windmill to help, these also distract

An option for what you can use (and what to avoid)

Local anaesthetics: a choice

- Topical anaesthetics has been shown to reduce injection pain
- If you choose to use topical anaesthetic, lidocaine-prilocaine (EMLA[™]) is available to buy from pharmacies for **around \$20** for a 5g tube:
 - Apply the cream **60 minutes before** the injections (check locations with your nurse before your appointment), cover with a plastic dressing. **Over 1 year old** can use up to 5g (one small tube)
 - Cream may cause temporary reddening/whitening of skin, this is normal
- If there is a rash, talk to your doctor - it could be a reaction

Avoid paracetamol (Pamol[™]), ibuprofen (Nurofen[™], Fenpaed[™]), ice and cold spray before injection – these have not been proven to reduce injection pain in young children and the medicines may affect the immune response. After injection paracetamol or ibuprofen may be used to relieve distressing localised pain.

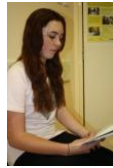
These are scientifically proven ways of reducing pain or distress in children during injections. Think about what worked and plan ahead to make the next vaccination less painful. These techniques can also be useful for blood tests and other minor medical procedures (please check with your health professional).

Helping manage your vaccinations A New Zealand guide (Age 11 and over)

Vaccine injections can sometimes be stressful and uncomfortable but there are things you can do to help. Plan ahead to work out what options you want to try:

1. Bring a distraction – like a magazine, or electronic game.
2. You may be thinking about what will happen:
 - You will get the vaccine in the arm
 - There may be a pinch or pressure for a few seconds
3. One choice is EMLA[™], a topical anaesthetic cream to numb the skin – you can buy this medicine at a pharmacy without a prescription for about \$20. If you don't choose this option you can still try some of the other strategies.
4. Read the 3 tips of pain management below, you can combine any of these strategies to improve pain relief.

What you can do



Sit upright

- Sit upright
- Some people prefer to look away during the injection

Vibration on the skin

- Vibration on your arm near the injection site right before and during injections can create 'white noise'. Some clinics may have a vibration device which works in this way.
- Do not rub the injection site afterwards

How you can act



Breathe deeply

- If you are nervous, take a few slow, deep breaths to calm yourself before and during injection – breathe so your stomach expands, not your chest



Distraction

- Distract yourself before the injection, and continue during and after injection
- Distractions such as books, toys, or electronic games are good. If those aren't available talking, humming, counting or trying to say the alphabet backwards may help.
- Blowing can be useful. Pretend you are blowing out birthday candles or blowing bubbles.

An option for what you can use (and what to avoid)



One option is topical anaesthetic

- Topical anaesthetics have been shown to reduce injection pain
- If you choose to use topical anaesthetic, lidocaine-prilocaine (EMLA[™]) is available to buy from pharmacies for around \$20 for a 5g tub:
 - Apply to upper outer part of the arm for 60 minutes before the injection – check product instructions (check locations with your nurse ahead of your appointment) cover with a plastic dressing. Can use up to 5g (one small tube).
 - You can use all of the 5g tube and cover with a plastic dressing
- Topical anaesthetics may cause temporary reddening/whitening of skin – this is normal
- If there is a rash, talk to your doctor- it could be an allergic reaction

Avoid paracetamol (Pamol[™]), and ibuprofen (Nurofen[™], Fenpaed[™]) – they have not been proven to reduce injection pain and they may affect the immune response. After the injection paracetamol or ibuprofen may be used to relieve distressing localised pain.

These are scientifically proven ways of making vaccine injections more comfortable. Think about what worked and plan ahead to make the next vaccination better. These techniques can also be useful for blood tests and other minor medical procedures (please check with your health professional).

There is little point in having the best science in the world if we can't communicate it effectively



Typologies

- Nuturers – children at low risk of disease
- Fearfuls – experience emotionally distressing
- Vulnerables – barriers to access
- Unwell - 'child poor health'
- Rejectors - opposed

Paediatric Vaccines Research Review

Making Education Easy

Issue 5 - 2011

In this issue:

- Pay-for-performance programme increases timely childhood immunisation
- Adverse events in pregnant women after influenza vaccination
- Helping mothers prevent influenza illness in their infants
- Effectiveness of influenza vaccination delivered to children at school
- Efficacy of quadrivalent HPV vaccine in males
- Local reactions to fifth dose of DTap vaccine
- Pneumococcal conjugate vaccine suppresses asthma in mice
- Recombinant MenB vaccine in infants
- Imperfect vaccine-induced whooping cough immunity
- Immunisation arguments in NZ print media: fact or fallacy?

Welcome to the latest edition of *Paediatric Vaccines Research Review*, a quarterly New Zealand publication bringing you some of the most important paediatric vaccine research from around the world. The Review provides summaries of 10 recent studies, each accompanied by a comment from either Dr. Nikki Turner or Helen Petousis-Harris on why it is important and how it can potentially affect practice. The Review also provides website links to the abstract or fully published paper so you can make your own judgements.

Highlights this month include reassuring data of the safety of the influenza vaccine in pregnant women, impressive results from a study of the quadrivalent HPV vaccine in males, and exciting signs that intranasal PCV7 vaccine might suppress asthma.

If you have colleagues within New Zealand who would like to receive *Paediatric Vaccines Research Review*, please send us their contact email and we will include them next time. We hope you find this edition interesting and look forward to hearing your comments.

Kind regards,

Dr Chris Tofield

Medical Advisor, Research Review
christofield@researchreview.co.nz

Improving timely childhood immunizations through pay for performance in Medicaid-managed care

Authors: Chien AT et al

Summary: This study evaluated the impact of a pay-for-performance (P4P) programme designed to reward timely immunisation delivery to 2-year-olds. In 2003 the Hudson Health Plan (a not-for-profit Medicaid-focused managed care plan) introduced a scheme whereby it paid a bonus of \$US200 for each fully immunised 2-year-old. Immunisation rates within Hudson Health Plan rose at a higher rate than those in comparison health plans. Supplementary analyses found that children with chronic conditions were more likely to be fully immunised during the study period as a result of the programme. In conclusion, a P4P programme can improve childhood immunisation rates.

Comment: Payment for performance (incentives) has been shown internationally to be effective in many contexts in healthcare. However in immunisation there is limited research published on effective strategies and designs. This study capitalised on a natural experiment in New York State, USA where one healthcare plan offered providers large financial remuneration and administrative support for timely immunisation rates, while others in the same region did not. These reimbursements amounted to 15–25% above base reimbursement for the care of 0- to 2-year-olds. It is no surprise that this was effective, however it was modest. Importantly it did not also exacerbate disparities. However the question for me would be whether this is the best use of a considerable amount of resources, and how effective interventions of this nature would be if they were of a lesser amount? NT

Reference: *Health Services Research* 2010;45 (6p2):1934-1947

<http://dx.doi.org/10.1111/A.1475-6773.2010.01168.x>

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