Experience with pneumococcal conjugate vaccines in New Zealand

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THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

50 MEMORABLE YEARS

Declaration

- Some of the data in this presentation is from an investigator led study funded by GSK
- I have served on Advisory Groups to GSK, Merck, and Pfizer; any honorarium goes to the institution

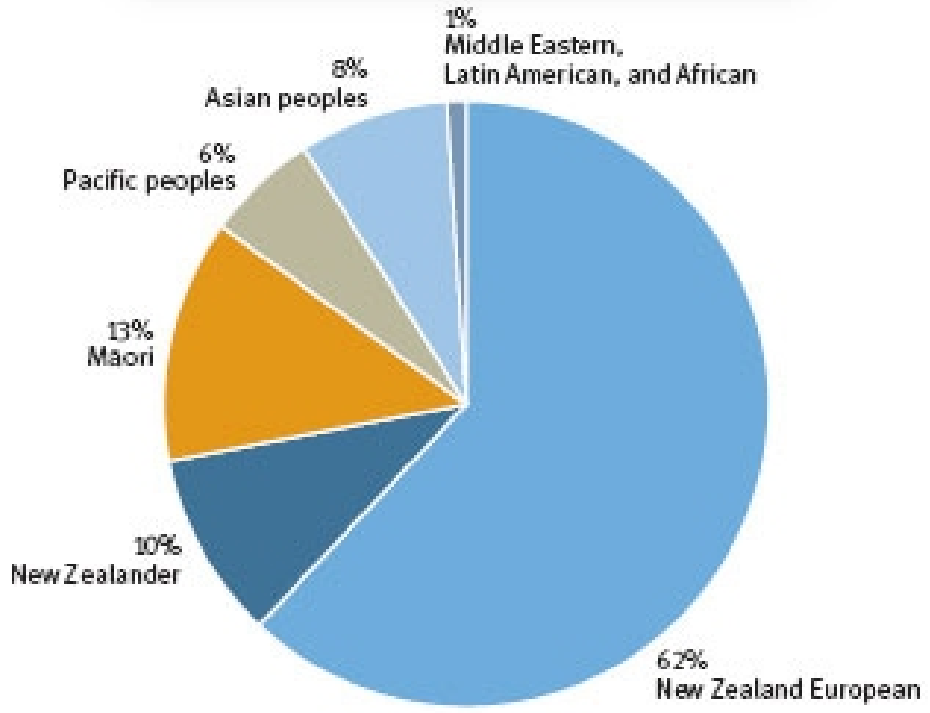
Presentation overview

- Uptake of pneumococcal vaccines in NZ during three periods
- Impact on IPD, all-cause pneumonia, otitis media (through various lenses)
- Consideration of 19A
- Effect of pneumococcal vaccines on sociodemographic disparities

IPD, invasive pneumococcal disease

New Zealand

- 4.8m, ethnically heterogeneous
- Disparities in health
  - Ethnic and socioeconomic
- GDP rank 53rd, 2nd most prosperous
- Maori and Pacific ethnicities disproportionately higher deprivation
  - Economic, health, housing, education…



Infectious diseases in NZ and introduction of PCVs

New Zealand has a high burden of infectious diseases and major ethnic inequities

Rates of serious bacterial infections and respiratory diseases: International comparisons

Disease	Other OECD countries: relative rate	NZ: relative rate
Rheumatic fever	1 (OECD)	13.8
Serious skin infections	1 (USA, Australia)	2
Whooping cough	1 (UK, USA)	5–10
Pneumonia	1 (USA)	5–10
Bronchiectasis	1 (Finland)	7

Craig E, et al. NZCYES: Indicator Handbook. 2007; Craig E, *et al*. NZCYES Report 2011

In New Zealand, Maori and Pacifica children carry this burden

Hospitalisations for serious bacterial infections and respiratory diseases in children and young people; risk by **ethnicity**, 2010–2014

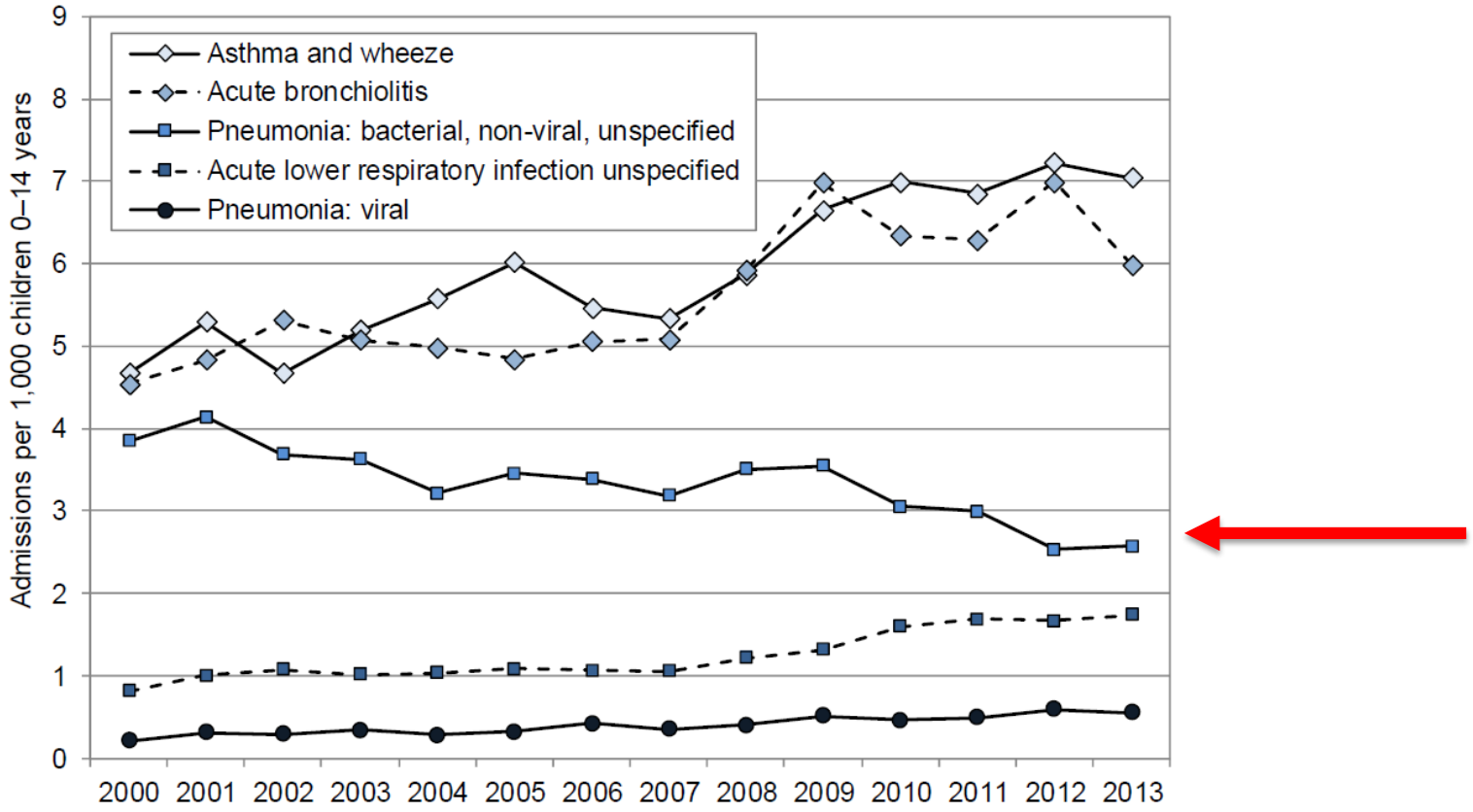
Cause of hospital admission	European	Māori	Pacific	Asian / Indian
Acute rheumatic fever[+]	1	33.07	70.42	0.77
Serious skin infection*	1	2.74	4.68	1.09
Pertussis[#]	1	2.09	2.58	0.32
Pneumonia[+]	1	1.91	4.16	1.06
Bronchiectasis[+]	1	7.94	10.28	1.09

*0–14 years; [+]0–24 yr; [#]<1 year

New Zealand Child and Youth Epidemiology Service, University of Otago; 2016. The health status of children and young people in New Zealand 2015. https://ourarchive.otago.ac.nz/handle/10523/7911 (accessed April 2018)

Respiratory infections have increased since 2000 among poorer children, with the exception of bacterial pneumonia

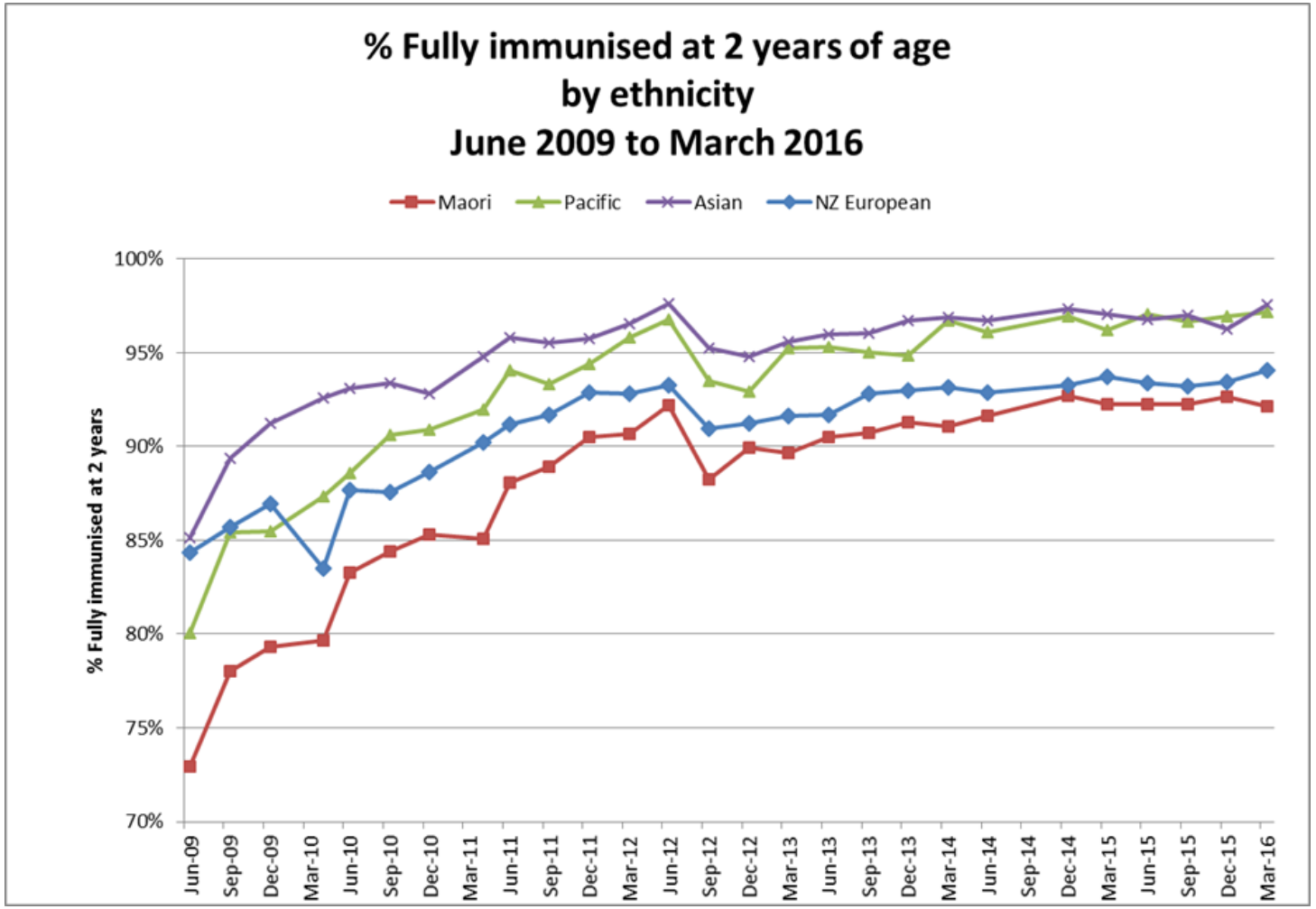
Hospital admissions for lower respiratory conditions with a social gradient in children aged 0–14 Years, New Zealand 2000–2013



Note: Acute and arranged admissions only

Child Poverty Monitor, 2013. Technical Report: hospital admissions and mortality with a social gradient. http://www.gena.co.nz/nzchildren/hospital_admissions.php (accessed April 2018)

New Zealand has improved its vaccine coverage by ~150% since 1997: Disparities in coverage are now negligible



New Zealand Ministry of Health, 2018. National and DHB immunisation data. https://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/immunisation-coverage/national-and-dhb-immunisation-data (accessed April 2018)

New Zealand introduced PCV7 in 2008

- PCV7 in 2008
- PCV10 in 2011
- PCV13 in 2014
- PCV10 in 2017

All in a 3+1 schedule

Concerns about 19A

Competitive tender

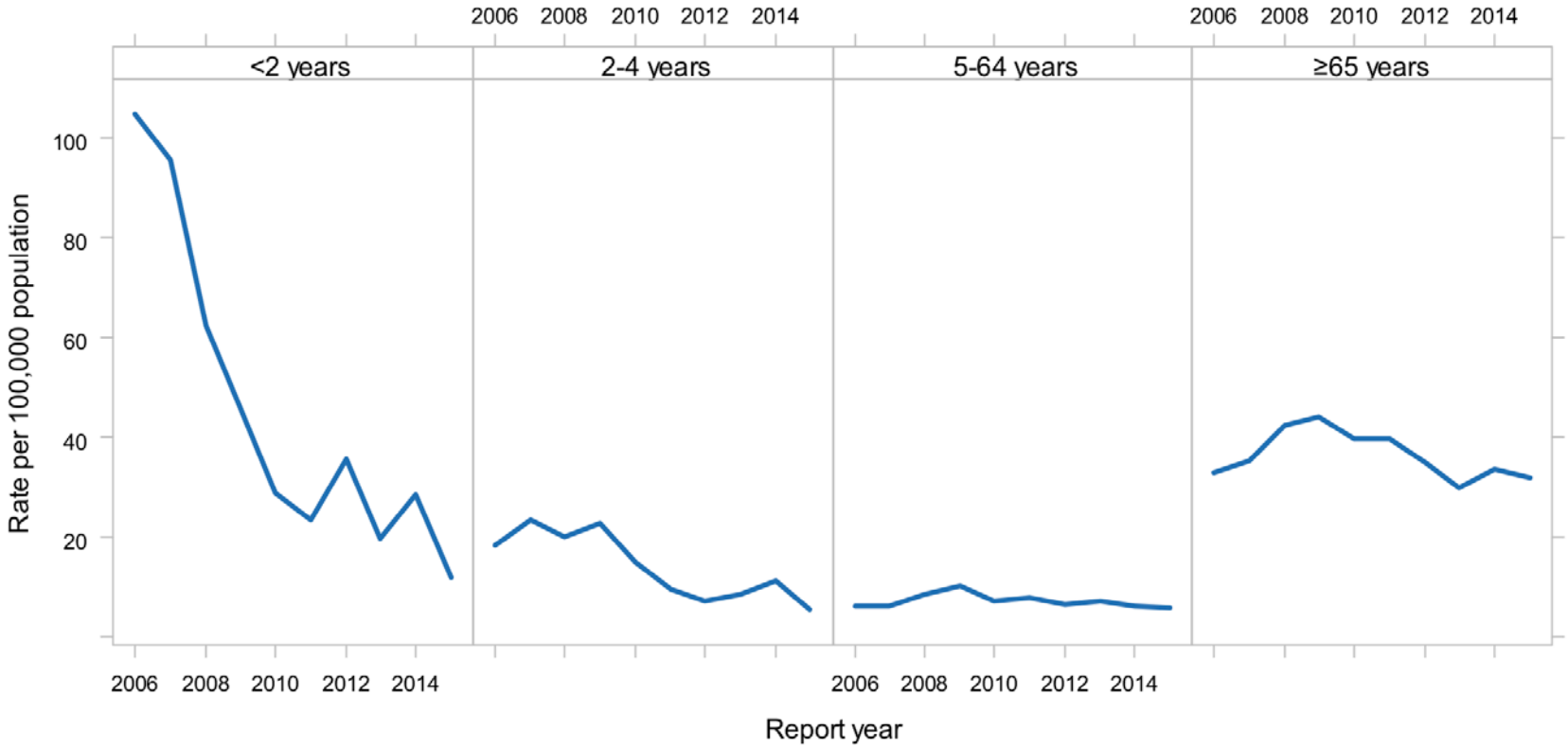
2015 Clinical review finds both vaccines suitable

New Zealand Ministry of Health, 2018. Immunisation Handbook. https://www.health.govt.nz/system/files/documents/publications/immshandbook-15-pneumococcal-disease-mar18-v2.pdf (accessed April 2018)

Impact of the PCV programme in NZ

IPD among NZ children <5 years has declined dramatically ☺

Rate per 100,000 population of IPD by age group and year, 2006–2015

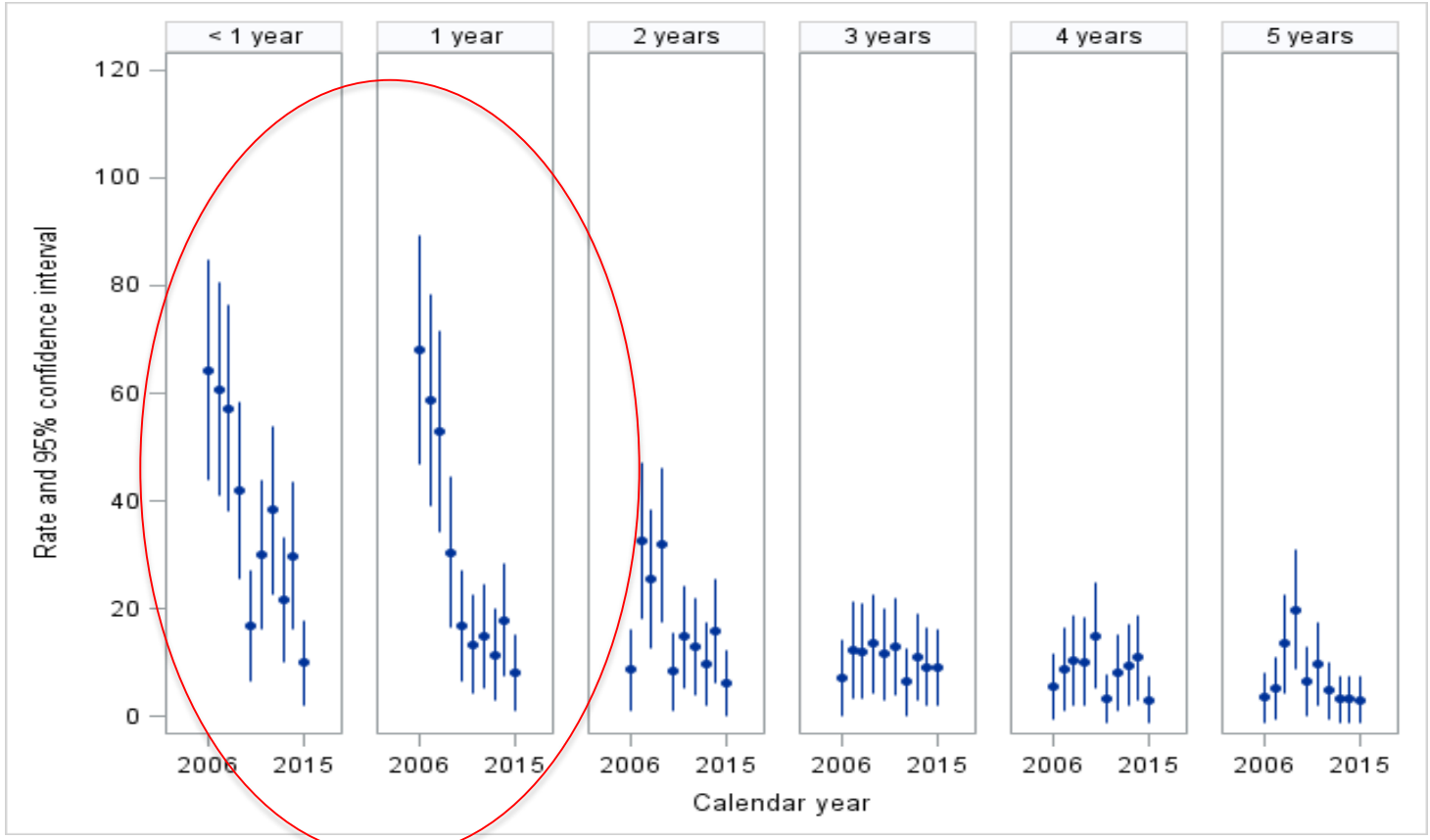


2018 < 2-years

- 1 case 1
- 1 case 19A
- 2 cases 3
- 21 cases non-PCV13

Note: Data presented for 2009 onwards is based on IPD notifications and data prior to 2009 is from ESR's national laboratory-based surveillance of IPD
New Zealand Ministry of Health, 2016. Surveillance report. Invasive pneumococcal disease in New Zealand, 2015.
https://surv.esr.cri.nz/PDF_surveillance/IPD/2014/2014IPDAnnualReport.pdf (accessed April 2018)

Initial IPD hospitalisation: The most significant declines in <2s



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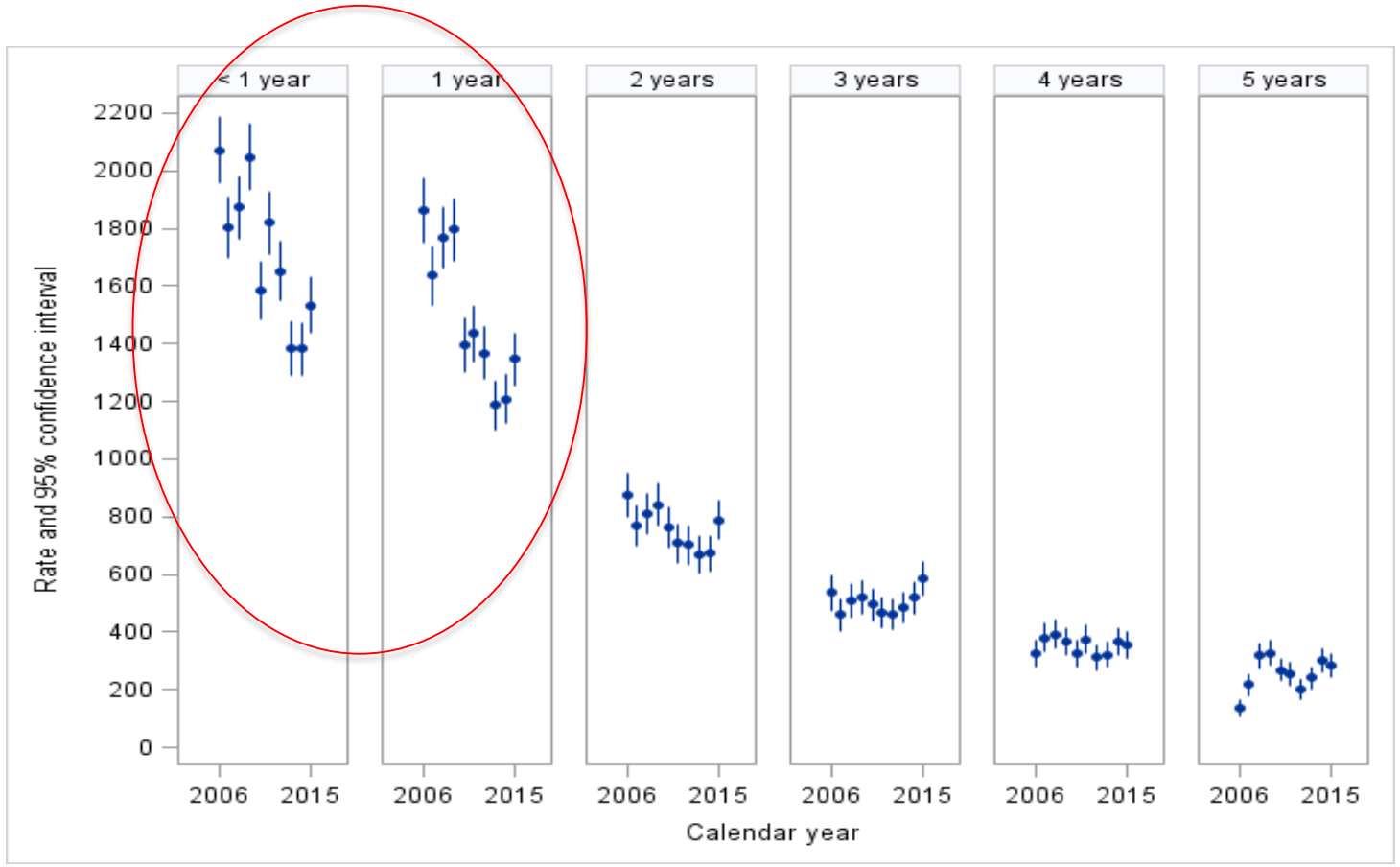
All cause pneumonia hospitalisation: The most significant declines in <2s



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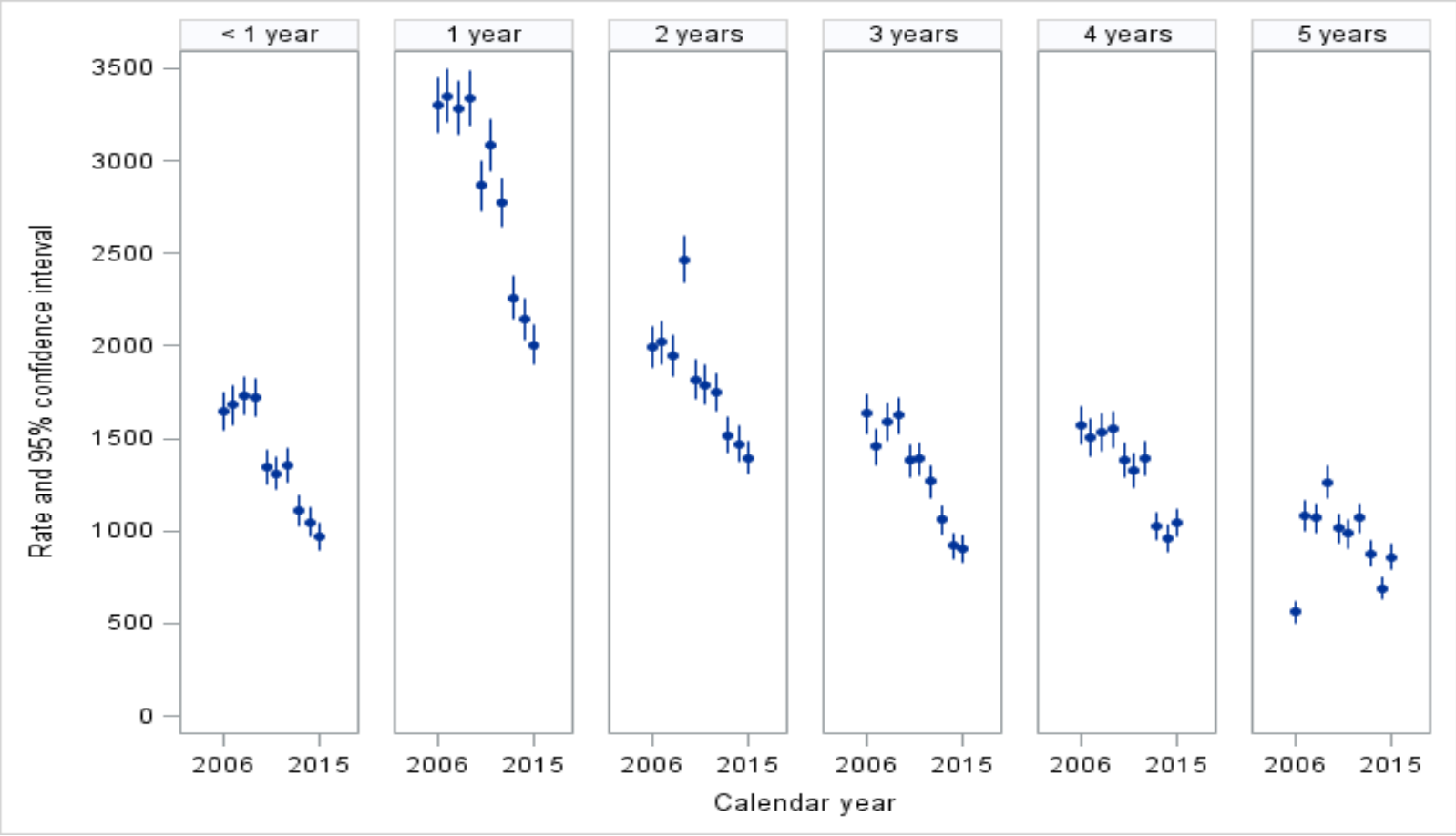
Otitis media: Significant declines in <5s



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Attempt at VE using indirect cohort method, IPD (2008–2013), aged <5 years

- VE was estimated as 1- (odds of vaccination in a VT case / odds of vaccination in a NVT case)[1]
- Limitations: numbers of cases of IPD in NZ now very low
  - Only 169 cases in 2008–2011 for PCV7 analysis
  - Only 39 cases in 2012–2013 for PCV10 analysis
- Diminishing case numbers for future analysis

NVT, non-vaccine type; VE, vaccine effectiveness; VT, vaccine type

1. Andrews N *et al. PLoS ONE* 2011;6:e28435

We measured VE, but ran out of IPD cases - a challenge for measuring PCV vaccine effects

Serotype of infection	Vaccinated at time of infection (≥2 doses)	Unvaccinated at time of infection
Vaccine serotype	11	44
Non-vaccine serotype	81	33
PCV7 vaccine effectiveness: 89.8% (77.9–95.3%)		

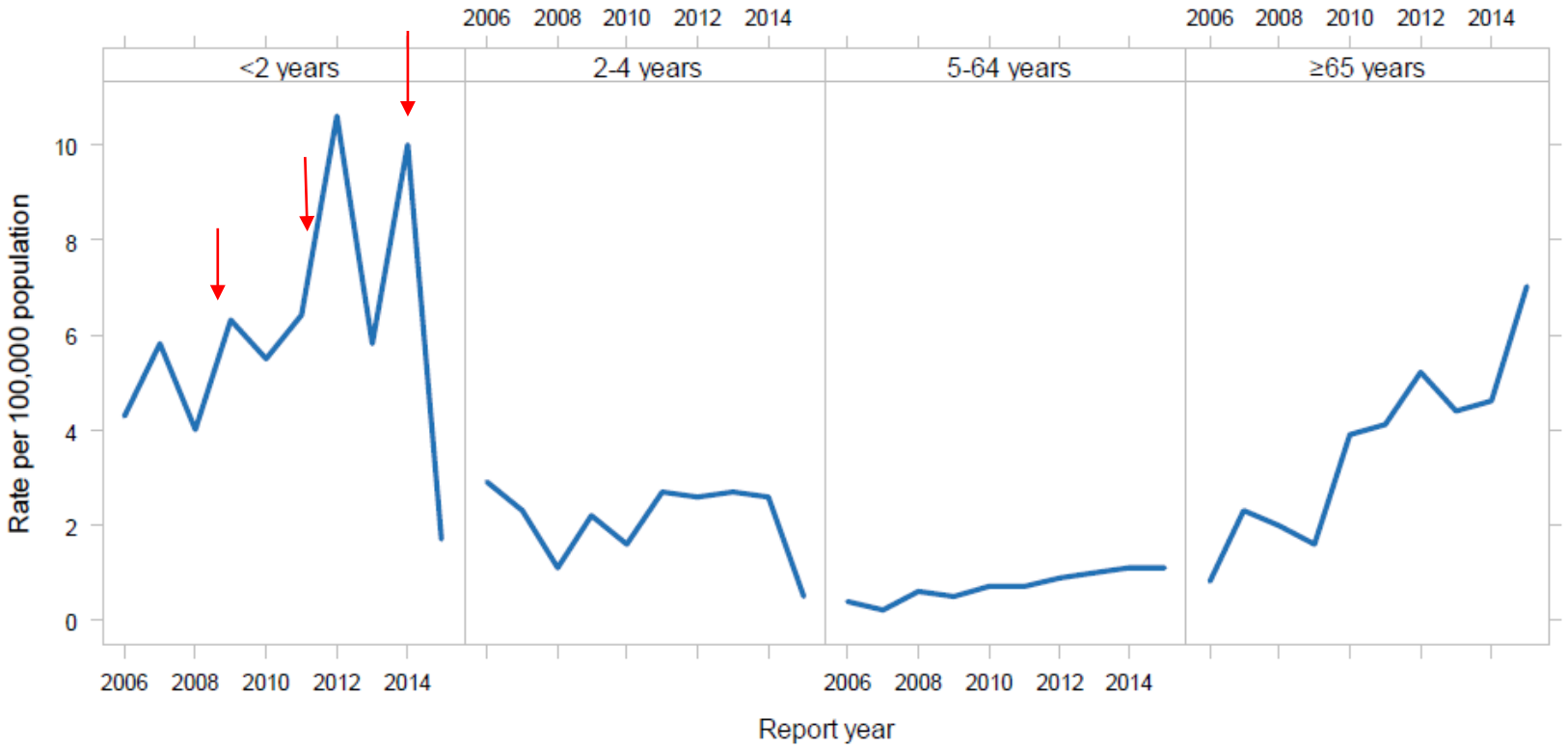
Serotype of infection	Vaccinated at time of infection (≥2 doses)	Unvaccinated at time of infection
Vaccine serotype	2	6
Non-vaccine serotype	21	10
PCV10 vaccine effectiveness: 84.1% (6.9–97.3%)		

Unpublished data. H Petousis-Harris and J. Paynter

What about 19A?

Serotype 19A: A general trend upward in older adults (2006–2014)

Rate per 100,000 population of IPD due to serogroup 19A
by age group and year, 2006–2014



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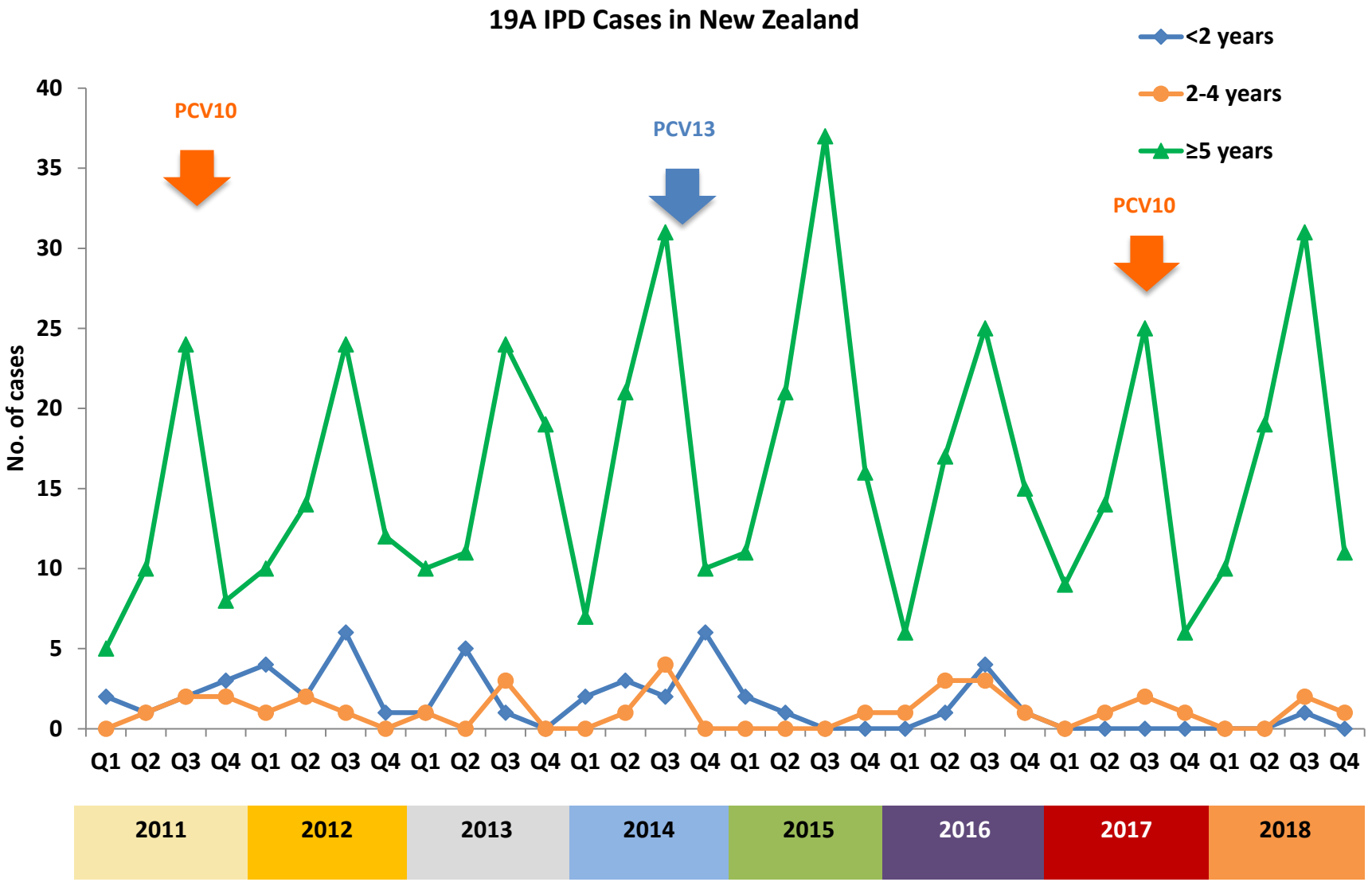
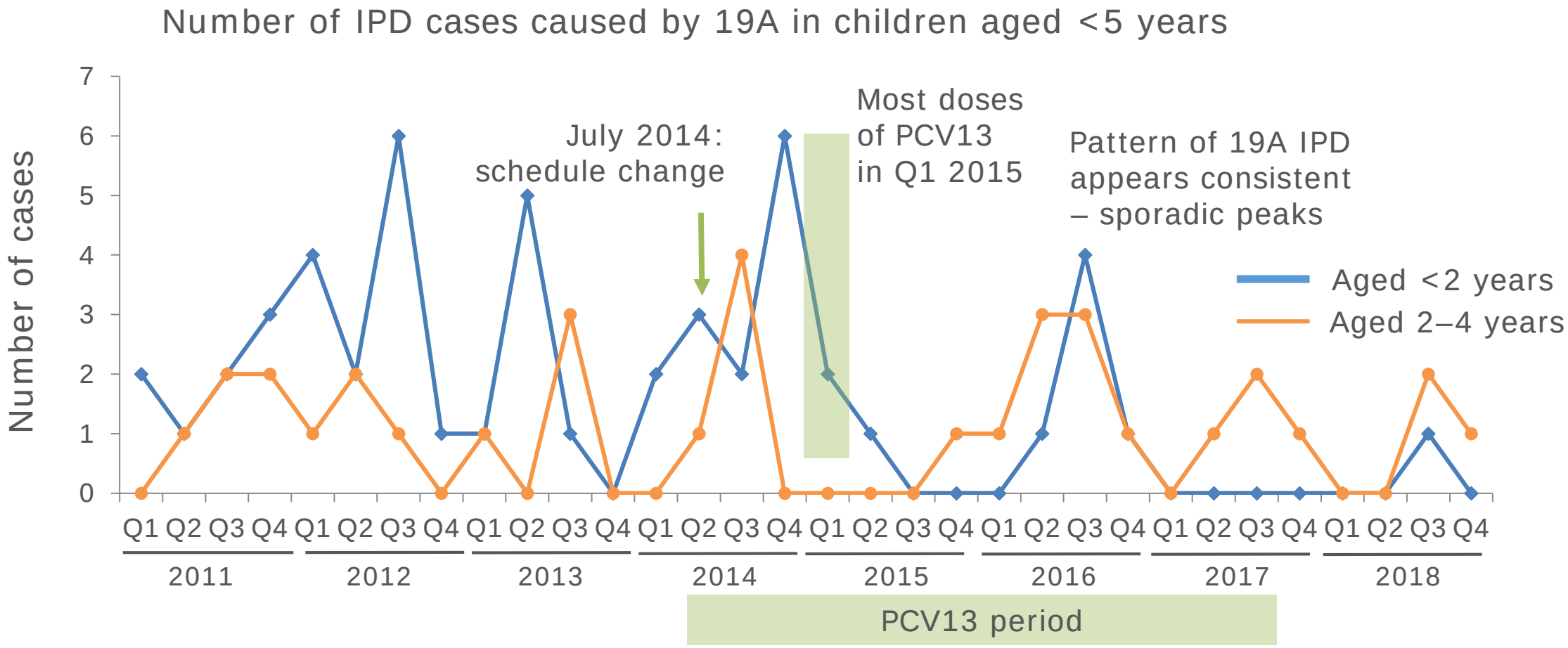

19A IPD Cases in New Zealand
<2 years
2-4 years
≥5 years
PCV10
PCV13
PCV10
No. of cases
40
35
30
25
20
15
10
5
0
Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4
2011
2012
2013
2014
2015
2016
2017
2018

Decline of 19A IPD occurred prior to change to PCV13 (2013–2018)

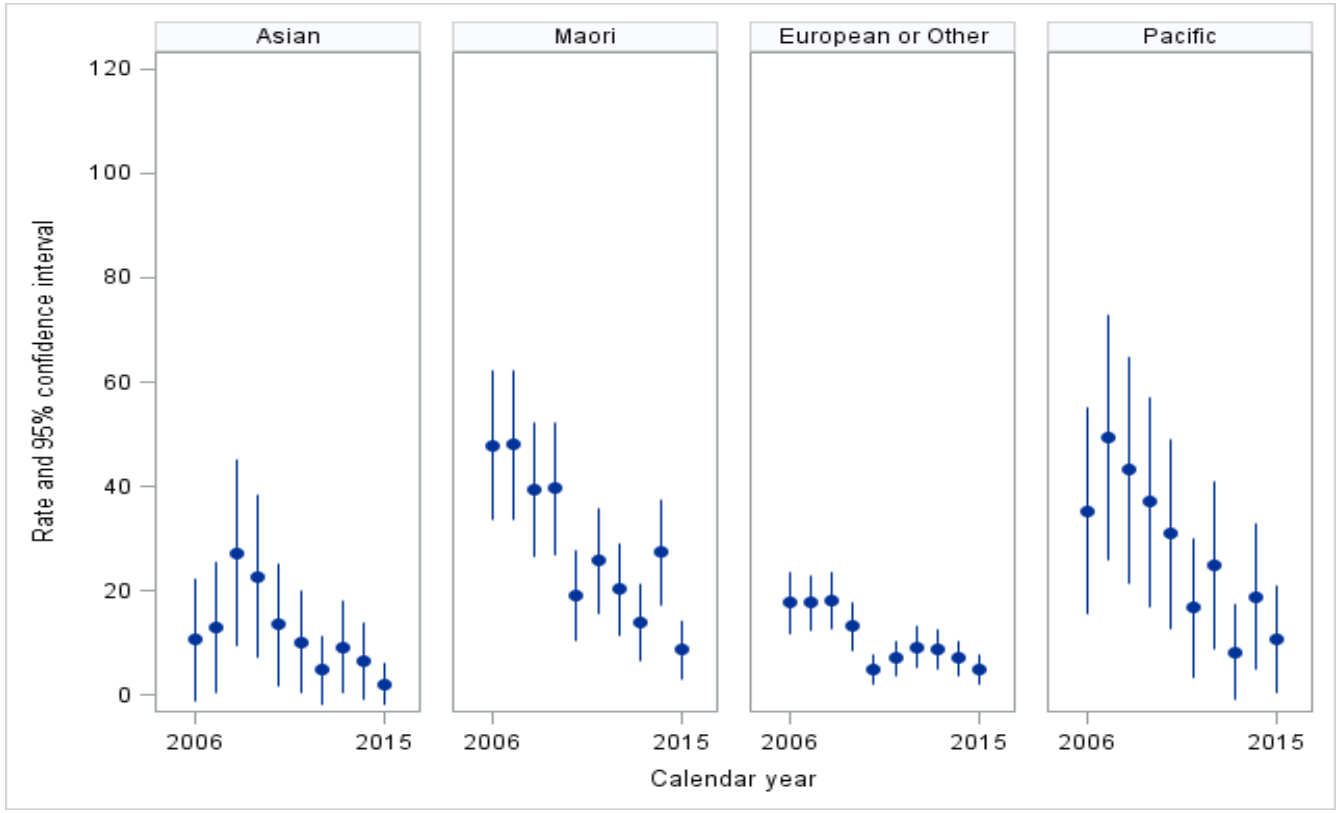


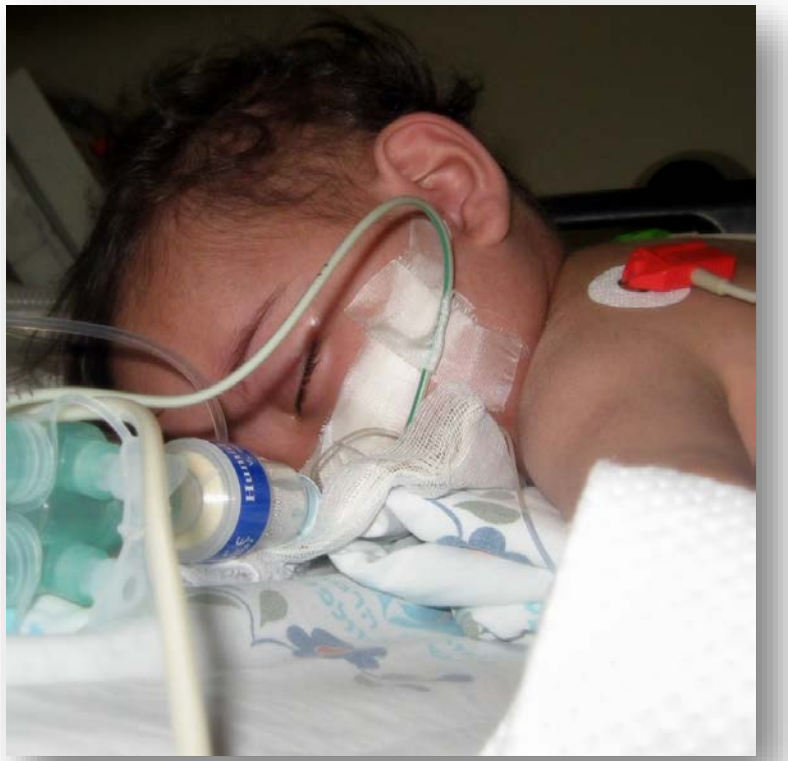
Data sourced from New Zealand Ministry of Health, 2013–2018. Invasive pneumococcal disease – quarterly reports. https://surv.esr.cri.nz/surveillance/IPD.php (all accessed April 2019)

Impact on sociodemographic inequities

IPD: significant reduction in ethnic disparities

IPD hospitalisation among children aged <6 years, by calendar year and ethnicity





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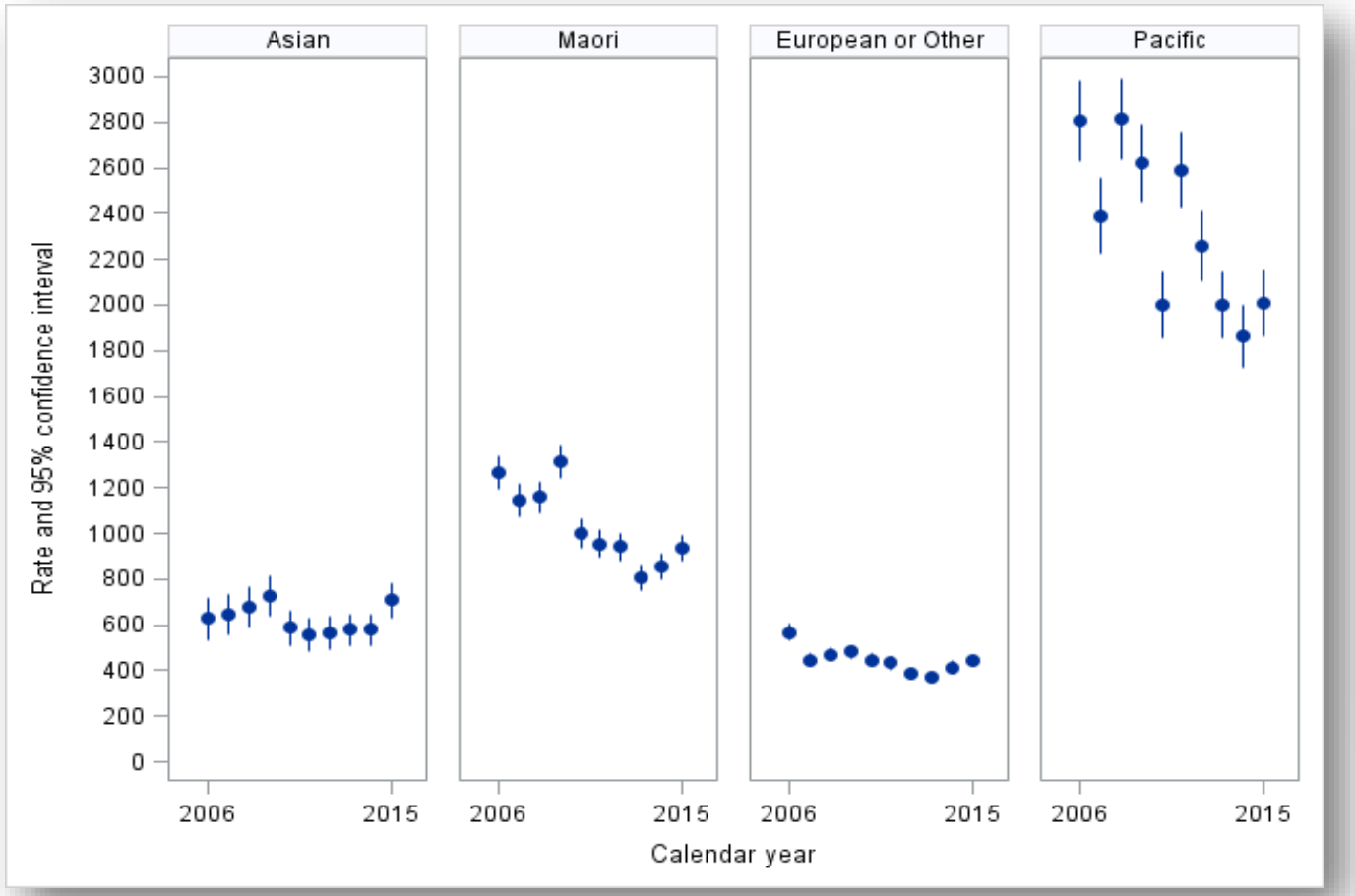
All cause pneumonia: significant reductions in ethnic disparities



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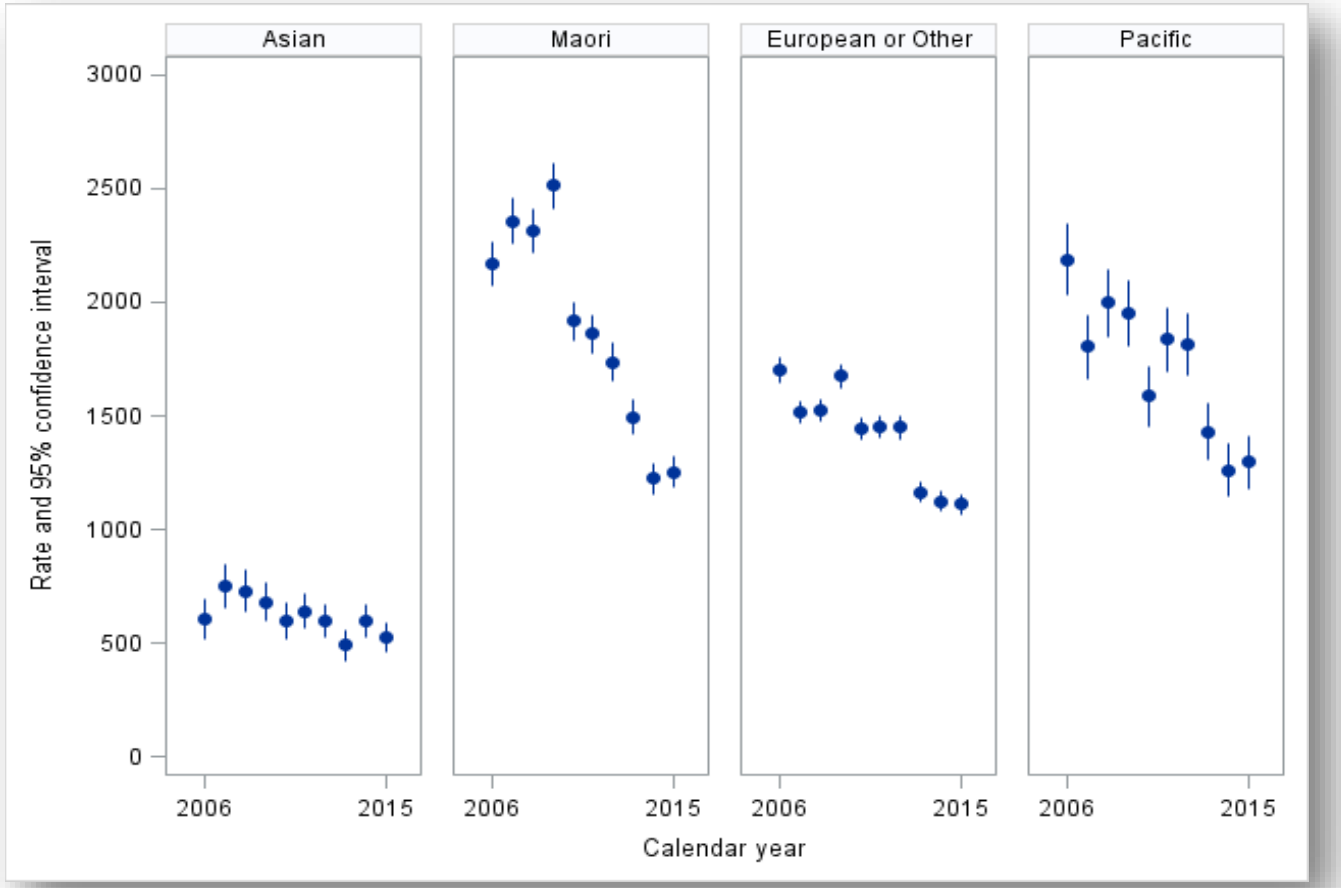
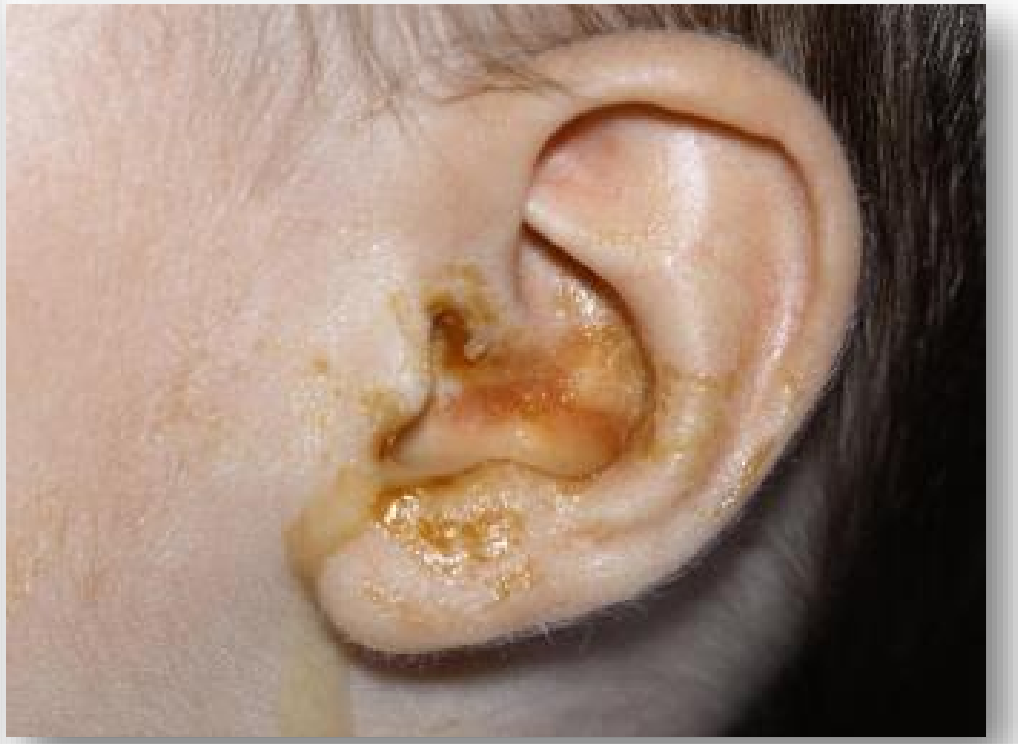
Otitis media related hospitalisations: significant reductions in ethnic disparities





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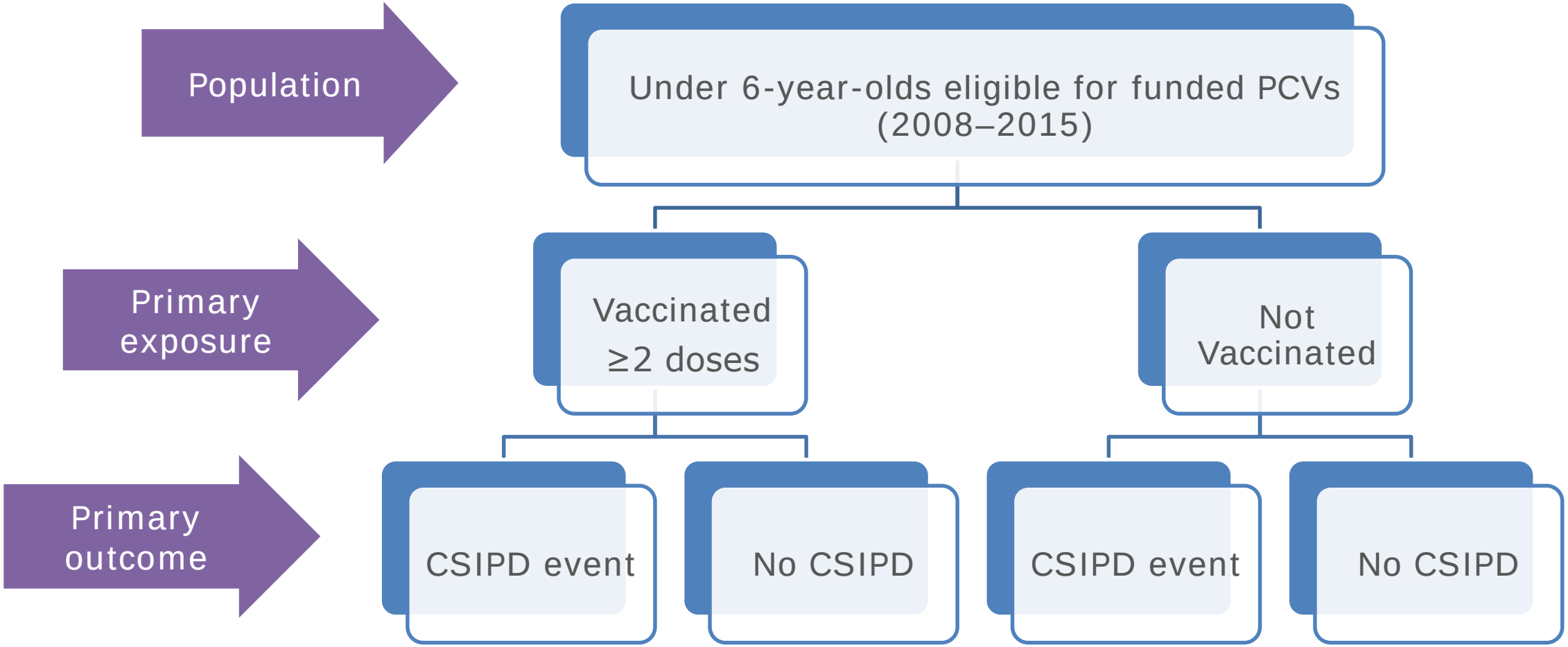
PCV effectiveness against clinically suspected IPD

Petousis-Harris D, Best E, Palmu A, Turner N, Howe A

Retrospective cohort study using data-linkage of national administrative datasets



VE=1-OR, Adjusted for sex, deprivation, prioritised ethnicity, District Health Board; CSIPD, clinically suspected IPD

Petousis-Harris D, Best E, Palmu A, Turner N, Howe A. PCV effectiveness against clinically suspected IPD. Poster. ISPPD. Melbourne. 2018.

Main outcomes

- Primary outcome of interest is non-laboratory confirmed CSIPD before 6 years of age
- CSIPD is determined by ICD-10 codes used in the FinIP study

Finnish study codes	
G00	Bacterial meningitis, not elsewhere classified
G00.1	Pneumococcal meningitis
A40.3	Sepsis due to S pneumoniae
G00.9	Bacterial meningitis, unspecified
B95.3	*S. pneumoniae* as the cause of disease classified elsewhere
A419	Sepsis unspecified
A40.9	Streptococcal Septicaemia unspecified
A49.9	Bacterial infection, unspecified
M00	Pyogenic arthritis
M001	Pneumococcal arthritis
M00.9	Polygenic arthritis, unspecified
I30.1	Infective pericarditis
B95.5	Unspecified streptococcus as the cause of disease classified to other chapters

International statistical classification of diseases and related health problems, 10th revision, 2016. apps.who.int/iris/bitstream/10665/246208/1/9789241549165-V1-eng.pdf (accessed April 2018)

Petousis-Harris D, Best E, Palmu A, Turner N, Howe A. PCV effectiveness against clinically suspected IPD. Poster. ISPPD. Melbourne. 2018

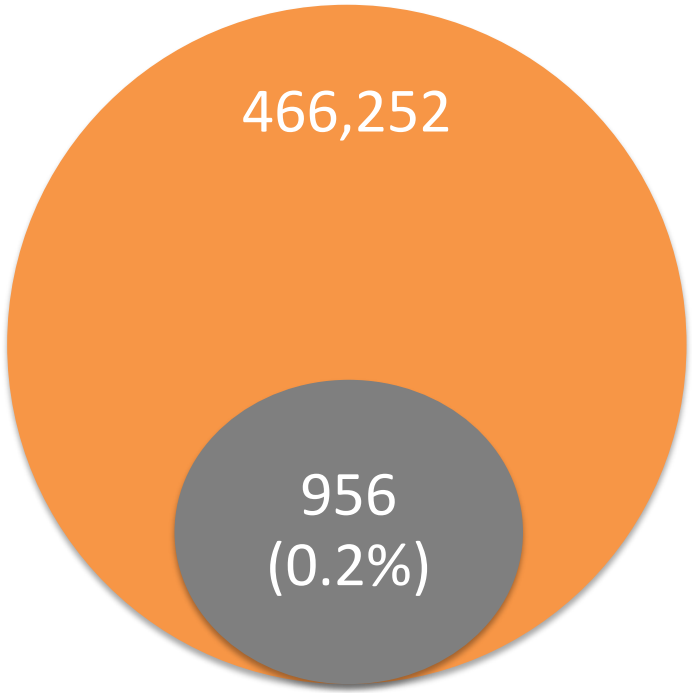
Cohort description, 2-dose definition. Reached most deprived the best

	Total sample	Vaccinated	Non-vaccinated
Number of individuals, n (%)	556,435	466,252 (84%)	90,183 (16%)
Sex, %			
Female	49%	84%	16%
Ethnicity, %			
Maori	22%	89%	11%
Pacific	11%	85%	15%
Asian	14%	79%	21%
NZEO	53%	83%	17%
Other	2%	52%	48%
Deprivation, %			
1 (Least)	18%	82%	18%
2	17%	83%	17%
3	18%	83%	17%
4	20%	84%	16%
5 (Most)	28%	85%	15%

Petousis-Harris D, Best E, Palmu A, Turner N, Howe A. PCV effectiveness against clinically suspected IPD. Poster. ISPPD. Melbourne. 2018

Results

Vaccinated

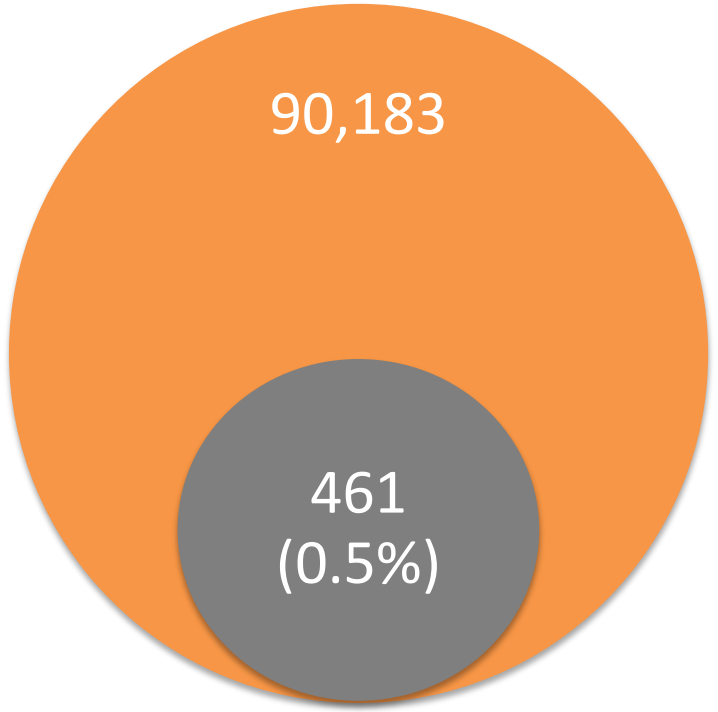


Adjusted vaccine effectiveness:
64% (95% CI 60–68)

Controlled for sex, deprivation, prioritised ethnicity, District Health region, year of vaccination

In a Finnish retrospective cohort study, vaccine effectiveness was estimated to be about **34%**[1]

Non-vaccinated



Petousis-Harris D, Best E, Palmu A, Turner N, Howe A. PCV effectiveness against clinically suspected IPD. Poster. ISPPD. Melbourne. 2018

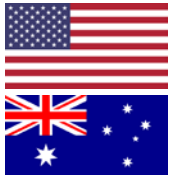
1. Palmu AA *et al. Pediatrics* 2015;136:e22–e27

VE varied by ethnicity and SES: higher in more deprived populations

	Number	Cases	VE (95% CI)
Ethnicity			
Maori	113,852	497	84% (81, 87)
Pacific	56,375	260	81% (75, 85)
NZEOA	346,284	617	54% (45, 62)
Socioeconomic status			
1 (least deprived)	91,469	156	46% (21, 63)
2	87,576	175	68% (56, 77)
3	91,268	205	62% (48, 72)
4	105,176	305	76% (69, 81)
5 (most deprived)	142,161	536	82% (79, 85)

NZEOA, New Zealand European, Other, and Asian

Petousis-Harris D, Best E, Palmu A, Turner N, Howe A. PCV effectiveness against clinically suspected IPD. Poster. ISPPD. Melbourne. 2018



USA and Australia

New Zealand

Lower effectiveness in indigenous peoples in USA and Australia

Higher effectiveness in Maori

?

Higher effectiveness in other ethnic minorities (people identifying as Black) USA

Higher effectiveness in other ethnic minorities (Pacific peoples)

✓

Higher effectiveness in higher deprivation groups in the USA

Higher effectiveness in higher deprivation groups

✓

Klugman *et al*. Pneumococcal Conjugate Vaccine and Pneumococcal Protein Vaccines. in Vaccines (2018) 7th Edition, , Naidu. *Communicable diseases intelligence quarterly report* 2012;37:S1-95. Pilishvili. *Journal of Infectious Diseases* 2010;201(1):32-41. de St Maurice Pediatrics 2015;136(5):e1186-e94. Scott *Journal of Infectious Diseases* 2012;205(2):280-88.
https://www.cdc.gov/abcs/reports-findings/surv-reports.html

Petousis-Harris D, Best E, Palmu A, Turner N, Howe A. PCV effectiveness against clinically suspected IPD. Poster. ISPPD. Melbourne. 2018

Are certain groups developing better immunity?

- This could be an effect of increased exposure in certain groups to pneumococcus younger in life, with the vaccines acting as a booster
  - This was seen to a small extent in the pre-licensure antibody titre studies[1]

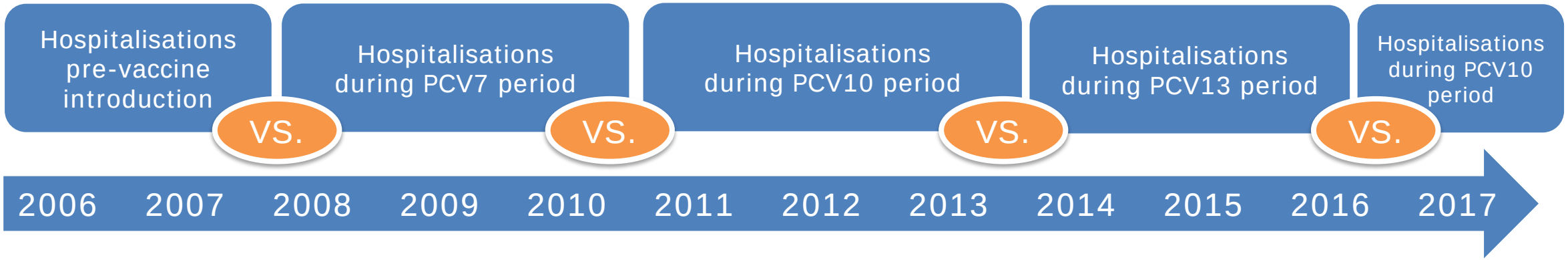
However, this doesn't fully explain the high disease rates and lower VE in international indigenous groups…

1. Siber GR, Chang I, Baker S, et al. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. Vaccine 2007;25(19):3816-26.

New Zealand has switched vaccine brand three times

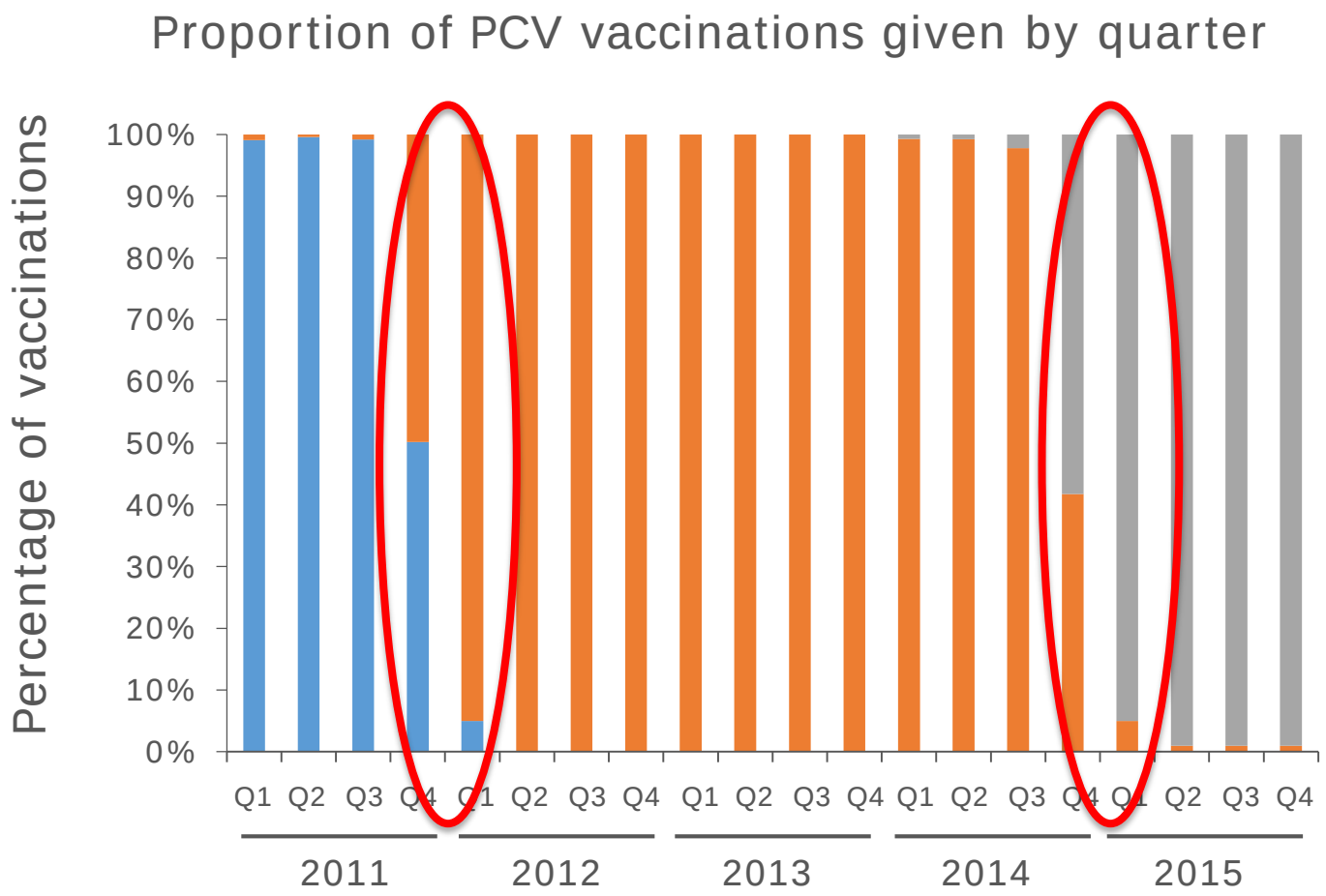
- PCV7 in 2008
- PCV10 in 2011
- PCV13 in 2014
- PCV10 in 2017

All in a 3+1 schedule



New Zealand Ministry of Health, 2018. Immunisation Handbook. https://www.health.govt.nz/system/files/documents/publications/immshandbook-15-pneumococcal-disease-mar18-v2.pdf (accessed April 2018)

Change in brand administered was phased in as stock of predecessor exhausted – resulted in a lag



Schedule changes dates and actual administration

- PCV10: July 2011 – Oct 2011
- PCV13: July 2014 – Dec 2014
- PCV10: July 2017 – ?

- N=~30,000 each period
- Can do head-to-head VE for ACP, OM and CSIPD

Data source: National Immunisation Register
Exposure determined using batch #

Conclusion

- PCVs have had a dramatic impact in New Zealand and have reduced sociodemographic disparities
- Not possible to draw conclusions about 19A, however considerable health gains expected through expansion of the NIP

Next steps

- Head-to-head VE study of vaccines using the PCV7-PCV10-PCV13-PCV10 transition periods
  - Pneumonia, OM, CSIPD

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NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

Thank you!

50 MEMORABLE YEARS

New Zealand National Immunisation Schedule from 1 April 2018

	RV	DTaP-IPV-HepB/Hib	PCV	Hib	VV	MMR	DTaP-IPV	Tdap	HPV	Td	Influenza	HZV
Every pregnancy								Boostrix® between 28-38 weeks pregnancy			Influvac® Tetra any trimester	
6 weeks	Rotarix®	Infanrix®-hexa	Synflorix®									
3 months	Rotarix®	Infanrix®-hexa	Synflorix®									
5 months		Infanrix®-hexa	Synflorix®									
15 months			Synflorix®	Hiberix®	Varilrix®	Priorix®						
4 years						Priorix®	Infanrix®-IPV					
11 years								Boostrix®				
12 years									Gardasil® 9 two doses			
45 years										ADT™ Booster		
65 years										ADT™ Booster	Influvac® Tetra	Zostavax®

VACCINE KEY

RV: rotavirus
DTaP-IPV-HepB/Hib: diphtheria, tetanus, acellular pertussis, polio, hepatitis B, *Haemophilus influenzae* type b
PCV: pneumococcal conjugate vaccine
Hib: *Haemophilus influenzae* type b
VV: varicella (chickenpox) vaccine
MMR: measles, mumps, rubella
DTaP-IPV: diphtheria, tetanus, acellular pertussis, polio
Tdap: tetanus, diphtheria, acellular pertussis
HPV: human papillomavirus
Td: tetanus, diphtheria
HZV: herpes zoster (shingles) vaccine

The Immunisation Advisory Centre

For more details, visit **immune.org.nz**

April 2018

- Rotavirus
- Diphtheria
- Pertussis
- Tetanus
- Hepatitis B
- Polio
- *Haemophilus influenza* type B
- Pneumococcal
- Measles
- Mumps
- Rubella
- Varicella
- HPV
- Zoster
- Influenza

- High risk
  - Meningococcal, BCG, PCV13
  - Maternal pertussis and flu

How did New Zealand decide to switch?

New Zealand Decision to switch

- The *Pharmacology and Therapeutics Advisory Committee (PTAC)* Immunisation Subcommittee considered submissions received by the *Pharmaceuticals Management Agency (PHARMAC)* from GSK and Pfizer for both pneumococcal vaccines in 2015.[1]
  - The Subcommittee considered that both of the submissions were of good quality, providing solid data which showed that the vaccines were efficacious.
  - The Subcommittee considered that both PCV10 and PCV13 are suitable for inclusion on the National Immunisation Schedule but that if PCV10 were listed for universal vaccination it may be necessary to continue to list PCV13 for vaccination of high risk groups.
- GSK won the tender following which:[2]
  - Synflorix will have Sole Supply Status in both the community and DHB hospital settings from 1 July 2017 until 30 June 2020.
  - Prevenar 13 (pneumococcal 13-valent protein conjugate vaccine (PCV13)) will remain funded for high risk patients only.

1. PTAC. Immunisation Subcommittee of PTAC, meeting minutes. 28 October 2015. Available at: https://www.pharmac.govt.nz/assets/ptacimmunisation-subcommittee-minutes-2015-10.pdf [accessed December 2018];
2. PHARMAC. Changes to National Immunisation Programme 2016. Available at: https://www.pharmac.govt.nz/news/notification-2016-07-28-immunisation-schedule/ [accessed December 2018

A competitive tender can result in savings that can be used to fund other health care priorities

- New Zealand switched from PCV10 to PCV13 in 2014[1]
  - Concerns about serotype 19A???[2]
- In 2015 a clinical review found that PCV10 and PCV13 are both suitable for inclusion in the national immunisation schedule but that if PCV10 were listed for universal vaccination it may be necessary to continue to list PCV13 for vaccination of high risk groups[3]
- In 2016 PCV10 won the tender[4]
  - Through a competitive procurement process and bundling of multiple vaccines[4]
  - Program savings meant New Zealand was able to also **introduce universal varicella vaccination and widen HPV vaccination access to people up to the age of 26**[4]

1. PHARMAC. Changes to National immunisation programme 2013. Availabe at: https://www.pharmac.govt.nz/assets/notification-2013-12-17-national-immunisation-schedule.pdf [accessed December 2016]; 2. PTAC. Immunisation Subcommitte PTAC, meeting minutes. 6 March 2013. Available at: https://www.pharmac.govt.nz/assets/ptac-immunisation-subcommittee-minutes-2013-03-06.pdf [accessed December 2016]; 3. PTAC. Immunisation Subcommittee of PTAC, meeting minutes. October 2015. Available at: https://www.pharmac.govt.nz/assets/ptacimmunisation-subcommittee-minutes-2015-10.pdf [accessed December 2016]; 4. PHARMAC. Changes to National Immunisation Programme 2016. Available at: https://www.pharmac.govt.nz/news/notification-2016-07-28-immunisation-schedule/ [accessed December 2016].

New Zealand public consultation (June 2016)

- PHARMAC acknowledges that there may be a small loss in health benefit from the change to PCV 10. However, the savings gained from this change and the health benefits gained from the widening of access to varicella and HPV vaccines are significant.
- The Immunisation Subcommittee of PTAC reviewed conjugated pneumococcal vaccines at its October 2015 and May 2016 (unpublished) meetings and considered that both PCV10 and PCV13 are suitable for inclusion on the National Immunisation Schedule. If PCV10 was listed, the Subcommittee recommended that PCV13 be listed for vaccination of high risk groups.
- Medsafe has recently approved an indication update for PCV10 (Synflorix), recognising protection against invasive pneumococcal disease (IPD) caused by serotype 19A pneumococcus. This indication has also recently been approved by the European Medicines Agency. The additional 19A indication is based on two post marketing studies on IPD in infants in Brazil (Domingues et al. Lancet Respir Med 2014;2:464-71) and Finland. Data from Quebec (Deceuninck et al (Vaccine 2015;33:2684-89) and clinical trials reporting on the immunogenicity of Synflorix also supported the change in indication.
- PHARMAC and the Immunisation Subcommittee also intends to monitor the incidence of serotype 19A.

PHARMAC. Changes to National Immunisation Programme 2016. Available at: https://www.pharmac.govt.nz/news/notification-2016-07-28-immunisation-schedule/ [accessed December 2018

PHARMAC (Pharmaceutical management agency)

Decides (on behalf of the district health boards) which medicines and pharmaceutical products are subsidised for community and hospital use

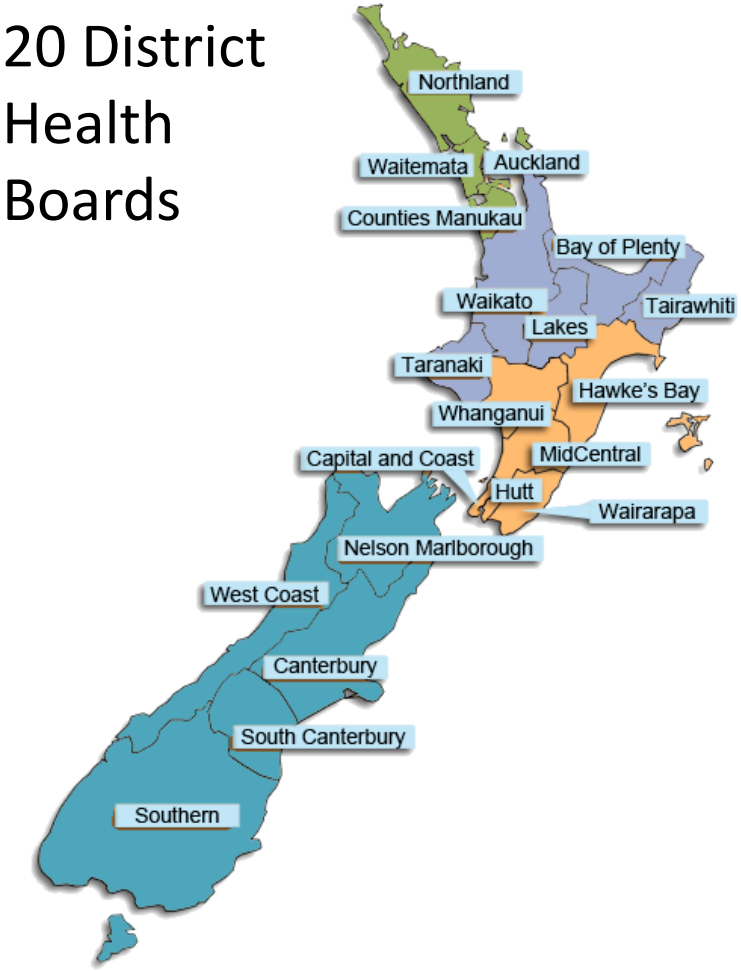
> *To secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided*

Since July 2012 took over the management of immunisation schedule and assessment of new vaccines

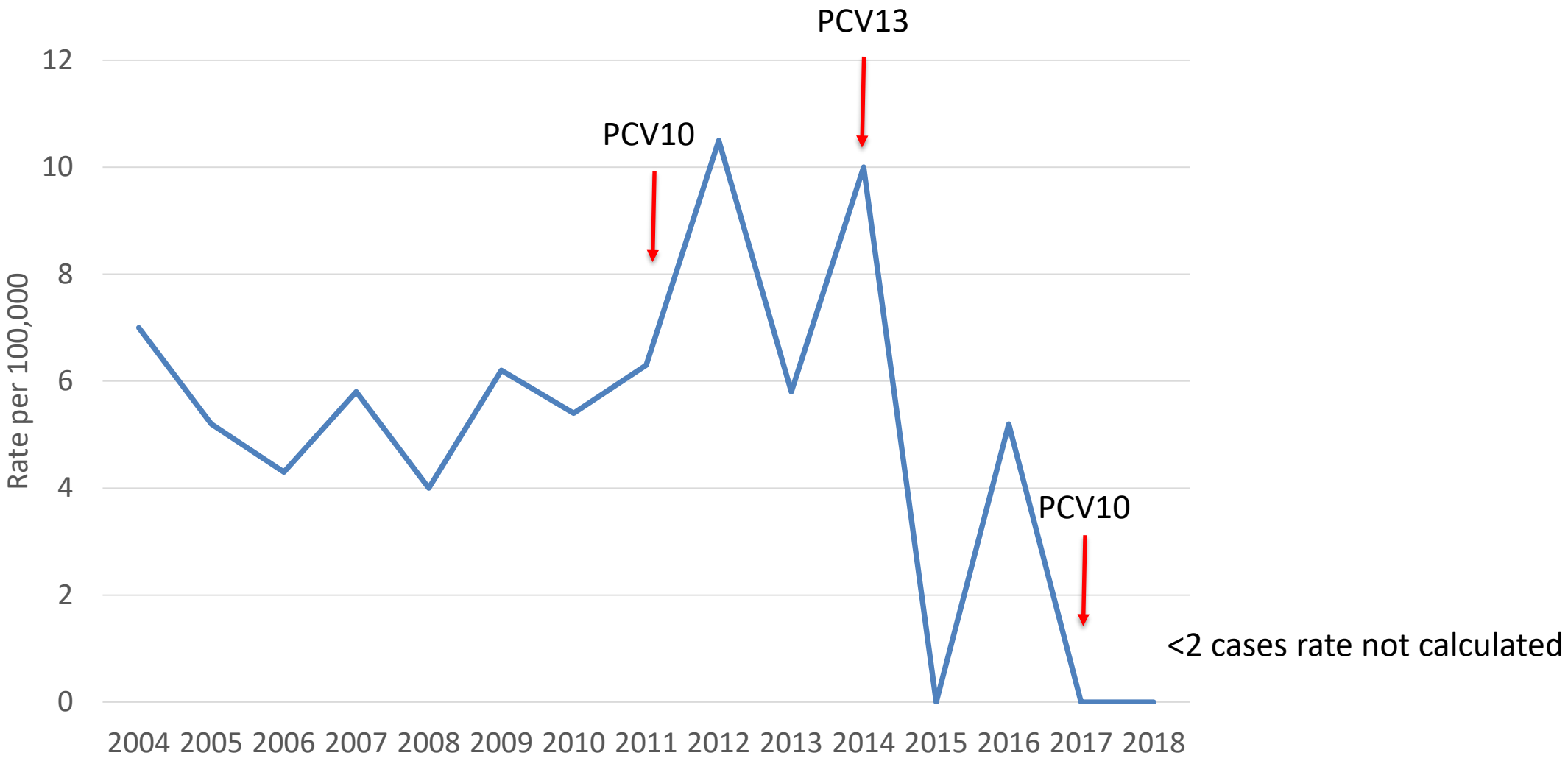
Allows for savings to be spent elsewhere

Advised by Technical Sub Committee

20 District Health Boards



Serotype 19A: Rate per 100,000 2004-2018 in under 2-years



Through competitive procurement and bundling of several vaccines NZ added varicella and extended the HPV programme

- Universal varicella programme
- Extension of HPV programme to include males
  - Gardasil 9 for all up to age 26 years