A cost benefit analysis of the use of routine serology in reducing the burden of re-immunisation post chemotherapy

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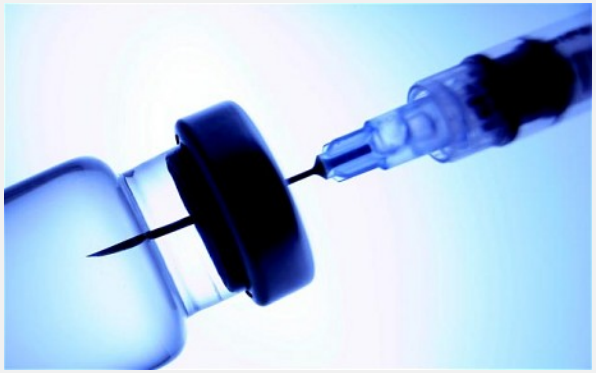
National Child Cancer Network NZ

Children's Cancer Research Trust

Why re-immunise after chemotherapy?

- Disease and therapy may lead to a loss of previously acquired immunity to vaccine preventable infections[1]
- The severity and pattern of loss of immunity varies with intensity of therapy but is not consistently predictable[2]



1. Januszkiewicz-Lewandowska et al, *Pediatric blood & cancer* (2015)
2. Ruggiero et al. *Pediatric blood & cancer* (2011)

Revaccination schedules

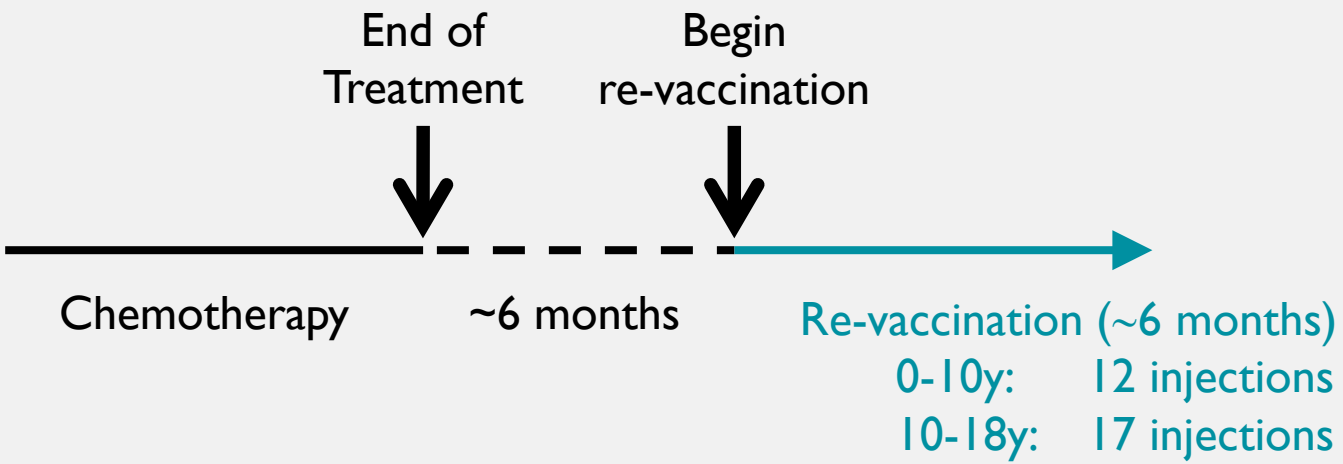
Either:

- Complete – all immunisations on schedule are given regardless of current immune status
  - Safety of vaccine administration to people who already have immunity has been proven[3,4]
- Targeted – perform serological testing for vaccine preventable diseases and revaccinations are given only to those required.
  - Multivalent vaccine preparations may reduce the number of vaccinations avoided

3. Rey et al. *Lancet* (2015)
4. Rodriquez *JGIM* (1995)

CHOC (Christchurch) Re-Vaccination Policy - Complete

Before 2014:



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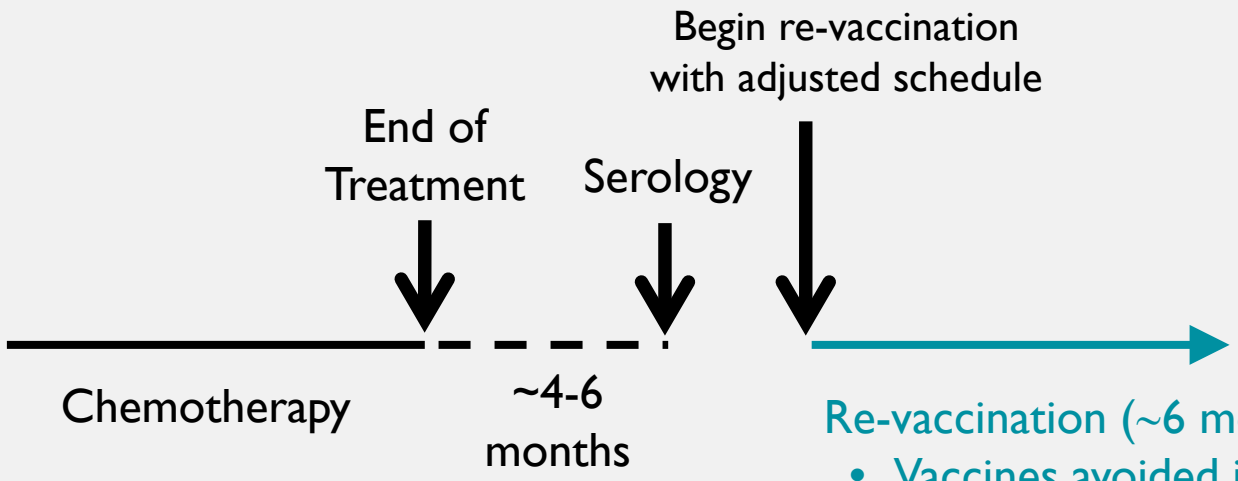
3. Rey Lancet 2015
4. Rodriquez JGIM 1995

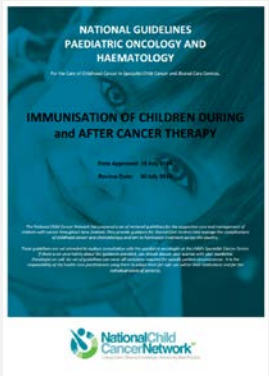
Starship (Auckland) Re-Vaccination Policy - Targeted



Re-vaccination (~6 months)

- Vaccines avoided if serology positive
  - 0-10y: Up to 12 injections
  - 10-18y: Up to 17 injections

Adopted as national re-immunisation policy in 2014:



Project timeline

Mar 2013	Decision to convene a national immunisation working group to harmonise the post-chemotherapy immunisation
Apr 2013	National immunisation schedule updated and decision to implement routine serology nationwide and collected results prospectively
Sep 2013	Research project proposal completed
Jun 2014	Ethics completed and data collection commenced
Jul 2016	Data collection completed
Jan 2017	Data analysis

Study Aims

1. To determine if routine serological testing at 4-6 months post chemotherapy treatment reduces the number of vaccinations required by children
2. If serological testing reduces the number of vaccinations required, determine if this results in an overall cost saving taking into account the upfront costs of serological testing.
3. Audit the compliance with the national immunisation policy
4. Document the relationship between serology at diagnosis and 4-6 months post treatment.

Inclusions and Exclusions

Inclusion Criteria:

- Received chemotherapy for a diagnosis of cancer
- Alive and in remission at 6 months from end of therapy
- ≤16 years at diagnosis
- <19 years at time of revaccination

Exclusion Criteria:

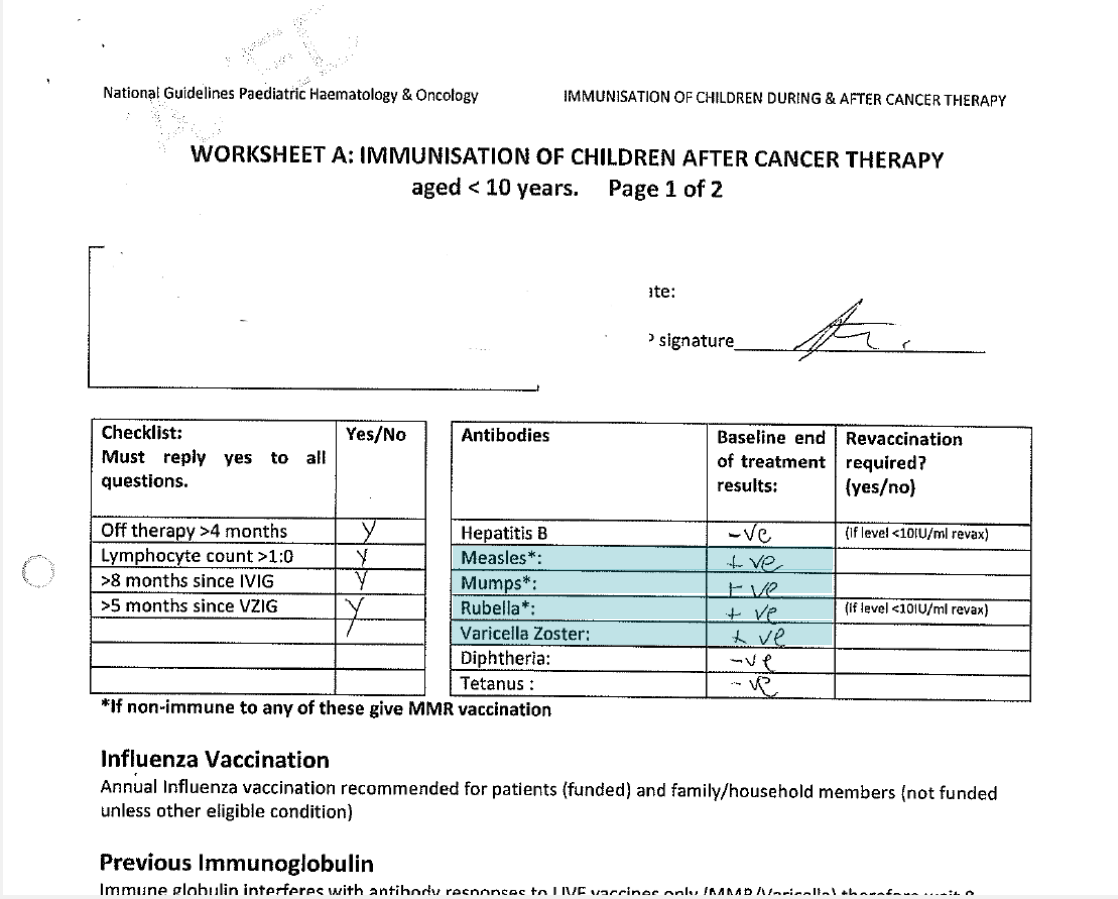
- Therapy included allogeneic stem cell transplant
- Therapy included anti B or T cell immunotherapy

Routine Serology Post-Chemotherapy

Varicella Zoster	IgG +/-	
Rubella	IgG	(neg <10IU/ml)
Mumps	IgG EIA +/-	
Measles	IgG EIA +/-	
Hepatitis B	anti-HBs	(neg <10IU/ml)
Diphtheria	Abs	(neg <0.163 IU/mL)
Tetanus	Abs	(neg <0.2 IU/mL)

Study Methods

1. Patients assessed as ready for pre-immunisation serology
2. Serology was obtained 4-6 months post-treatment
3. Results collected and individualised re-immunisation schedule sent to GP.



National Guidelines Paediatric Haematology & Oncology IMMUNISATION OF CHILDREN DURING & AFTER CANCER THERAPY

WORKSHEET A: IMMUNISATION OF CHILDREN AFTER CANCER THERAPY
aged < 10 years. Page 1 of 2

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Checklist: Must reply yes to all questions.	Yes/No
Off therapy >4 months	Y
Lymphocyte count >1:0	Y
>8 months since IVIG	Y
>5 months since VZIG	Y

Antibodies	Baseline end of treatment results:	Revaccination required? (yes/no)
Hepatitis B	-ve	(if level <10IU/ml revax)
Measles*:	+ve	
Mumps*:	+ve	
Rubella*:	+ve	(if level <10IU/ml revax)
Varicella Zoster:	+ve	
Diphtheria:	-ve	
Tetanus :	-ve	

***If non-immune to any of these give MMR vaccination**

Influenza Vaccination
Annual Influenza vaccination recommended for patients (funded) and family/household members (not funded unless other eligible condition)

Previous Immunoglobulin
Immune globulin interferes with antibody responses to LIVE vaccines only (MMR/Varicella) therefore wait 9

WORKSHEET A: IMMUNISATION OF CHILDREN AFTER CANCER THERAPY
aged < 10 years. Page 2 of 2

Paediatric Oncology years, months
GP: Dr Kelly/Lyver
ACC#: › signature
New Zealand
Ph:

Recommended Immunisation Schedule

GP must sign the sheet as all vaccines must be prescribed by a medical practitioner.
#Write "omit" if not indicated to receive vaccine

	Vaccines	Notes	Date given/omitted#	Vaccinator
1st Dose	**DTaP-IPV-HepB/Hib** (Infanrix-hexa)	Give as a booster even if immune to all antigens (now funded to age 10)		
	PCV-13 (Prevenar 13)			
4weeks later Date due:	**DTaP-IPV-HepB/Hib** (Infanrix-hexa)	use even if Hep B immune		
4 weeks later Date due	**PCV-13** (Prevenar 13) ***OR***	If less than 5 years		
	PPV 23 (Pneumovax)	If > 5 years. Revaccinate with PPV23 once more in 5 years' time only if risk persists		
	DTaP-IPV-HepB/Hib (Infanrix-hexa)	Give if HepB, Dip or Tet previously non-immune. Then check anti-HBsAg 1 month later. If negative (<10) re-immunise with 3 doses HBvaxPro 10µg at monthly intervals.		
4 weeks later Date due	**MMR**	Omit only if immune to all three diseases. Do not give within 5 months of VZIG or 8 months of IVIG		
	MCV4-D (Menactra)	If >2 years		
4 weeks later Date Due:	**MMR**	Omit only if immune to all three diseases Do not give within 5 months of VZIG or 8 months of IVIG		
	Varicella (Varilrix)	Omit if immune Do not give within 5 months of VZIG or 8 months of IVIG		
8 weeks later	**MCV4-D** (Menactra)	2nd dose		
	Varicella (Varilrix)	2nd dose Omit if previously immune Do not give within 5 months of VZIG or 8 months of IVIG		
At aged 4 years or over (booster)	**DTaP-IPV** (Infanrix-IPV)	give when at least 4 yrs old AND >12 months since last Infanrix-hexa		

→ **GP**

Data collection

- Patient demographics, cancer type and treatment
- Serology results used to determine number of vaccine avoided.
  - Compliance/errors in serology or schedule assessed separately.
- Re-immunisation records were crossed checked against the National Immunisation Register and/or GP records to assess compliance.
- Estimated cost of serology tests obtained from Canterbury Health Laboratories (2014) - $183 NZD per patient
- Costs of vaccines vials estimated from Ministry of Health and PHARMAC (some limited by commercial sensitivity)

Results – CHOC (Christchurch) patients only

85 patients ending treatment identified over a two year period (Jul 2014 – Jun 2016)

23 excluded:

- 8 patients – Serology was performed too late (after 30/6/2016)
- 3 patients didn't have chemotherapy (radiation therapy and/or surgery only)
- 3 patients were too young at diagnosis to have completed childhood vaccinations and therefore no need for post-treatment serology
- 3 patients either declined immunisations or follow-up in general
- 3 patients received rituximab
- 2 patients moved elsewhere for completion treatment - Australia
- 1 patient was too old at the end of treatment to fit criteria

62 included: 48% female, 52% male

Average age at serology: 9.3

Did serological testing prior to revaccination reduce the number of vaccinations required?

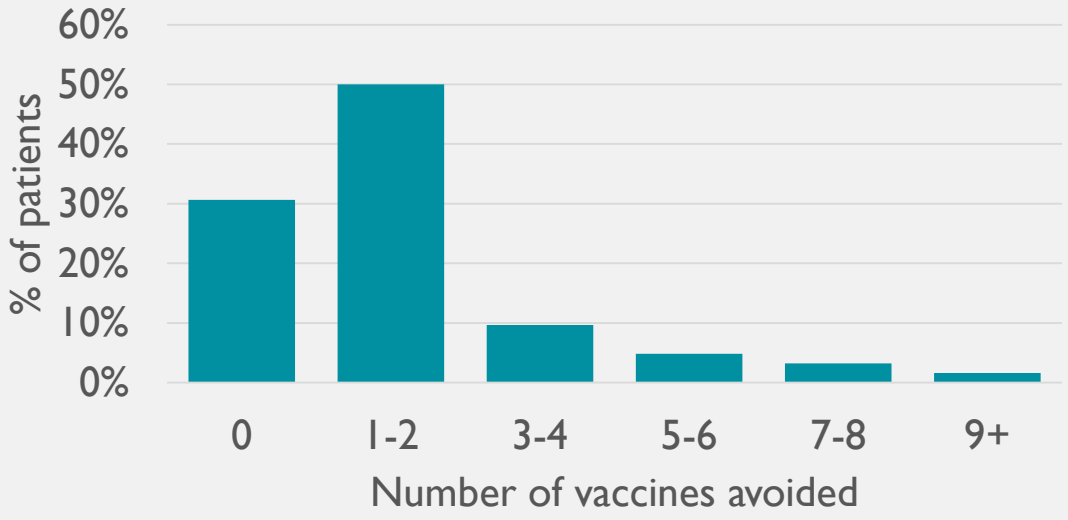
Yes

69% avoided at least one vaccination*

2.08 vaccines avoided per patient on average

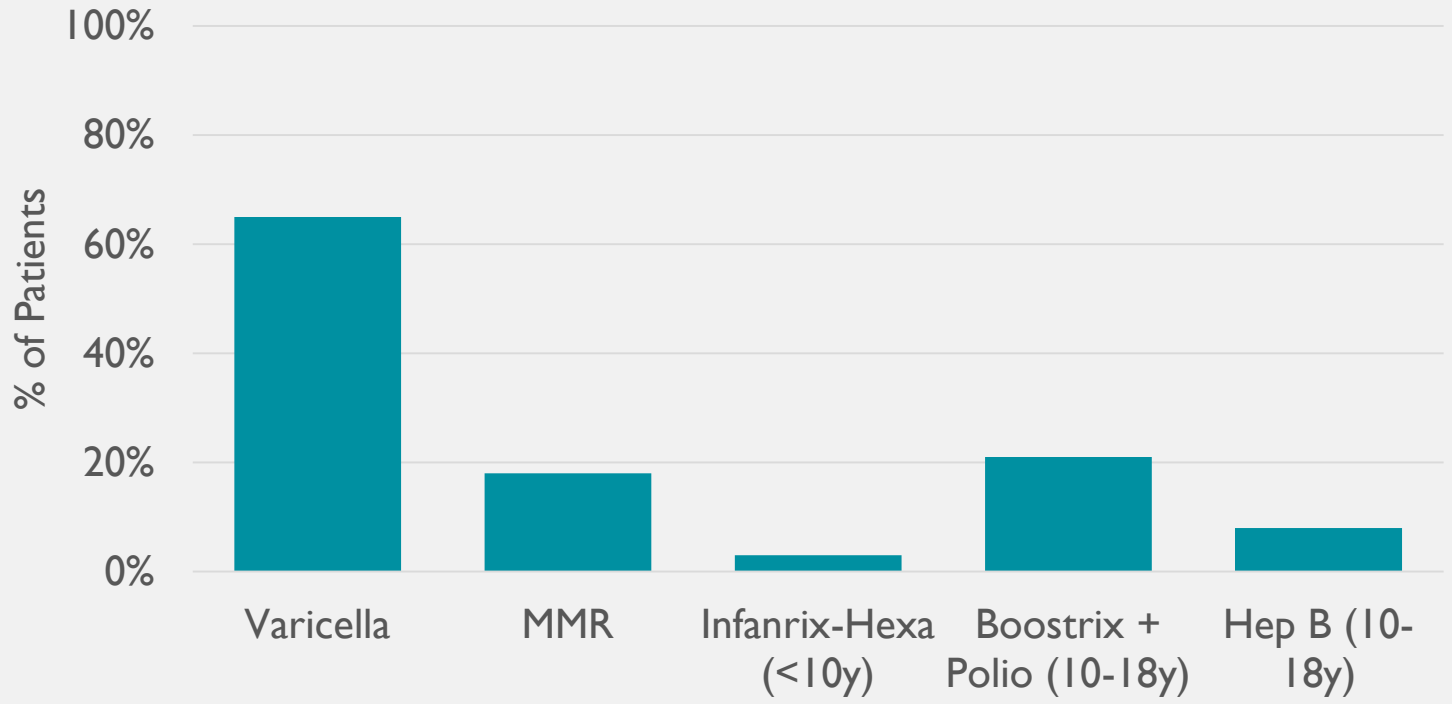
Average vaccines per patient reduced from 14 to 12

Average needle-sticks per patient reduced from 14 to 13



*vaccination refers to multivalent preparation where applicable

Vaccine Breakdown



MMR: **measles, mumps, rubella**

Infanrix-hexa: **tetanus**, **diphtheria**, **hepatitis B**, pertussis, polio, and *Haemophilus influenzae* (type b)

Boostrix: **tetanus**, **diphtheria**, pertussis

(**Bold** = immunity required to avoid vaccine)

Cost-Benefit Analysis

Does the reduction in vaccinations due to serological testing result in an overall cost saving taking into account the upfront costs of the tests?

Estimated* cost of serology (per 100 patients)
= $18,318 NZD

Estimated† cost *saving* from fewer vaccines (per 100 patients)
= $7,884 NZD

*Estimates based on 2014 CHL serological testing costs

†Estimates based on Ministry of Health and PHARMAC vaccination costs

Compliance with Re-Immunisation Policy

Correct serology performed: 86%

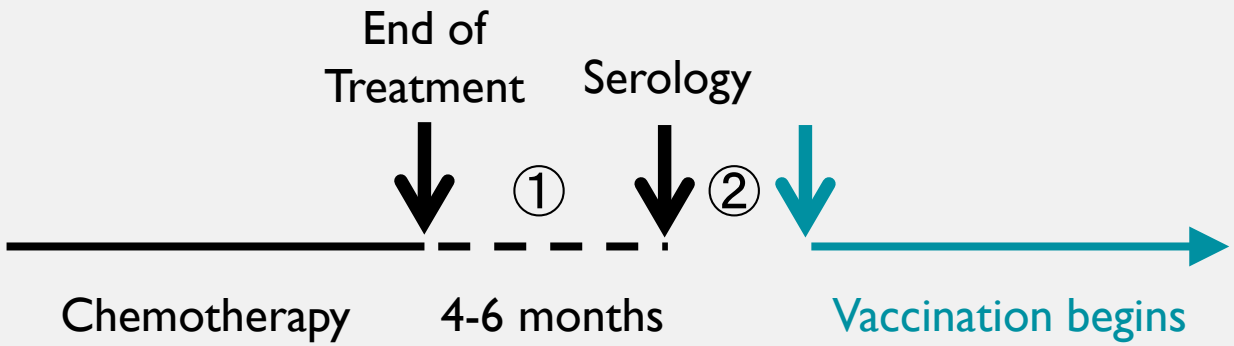
Immunisation schedule completed correctly: 78%

① Median time from EOT to serology *(aim 120-180)*: 172 days

Range (49-352)

② Median time serology to 1st injection: 69 days

Range (16-251)



Compliance with Re-Immunisation Policy

Correct serology performed: 86%

Immunisation schedule completed correctly: 78%

Median time from EOT to serology *(aim 120-180)*: 172 days
Range (49-352)

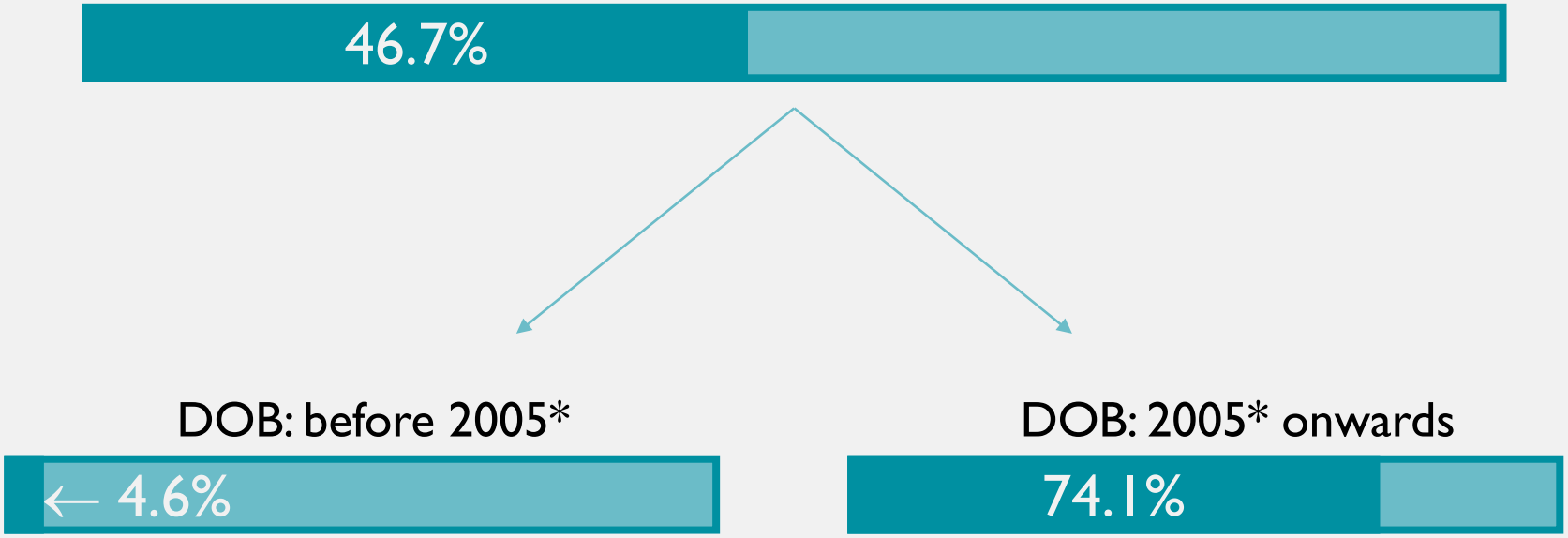
Median time serology to 1st injection: 69 days
Range (16-251)

All vaccines received as per schedule: 68%

National Immunisation Register

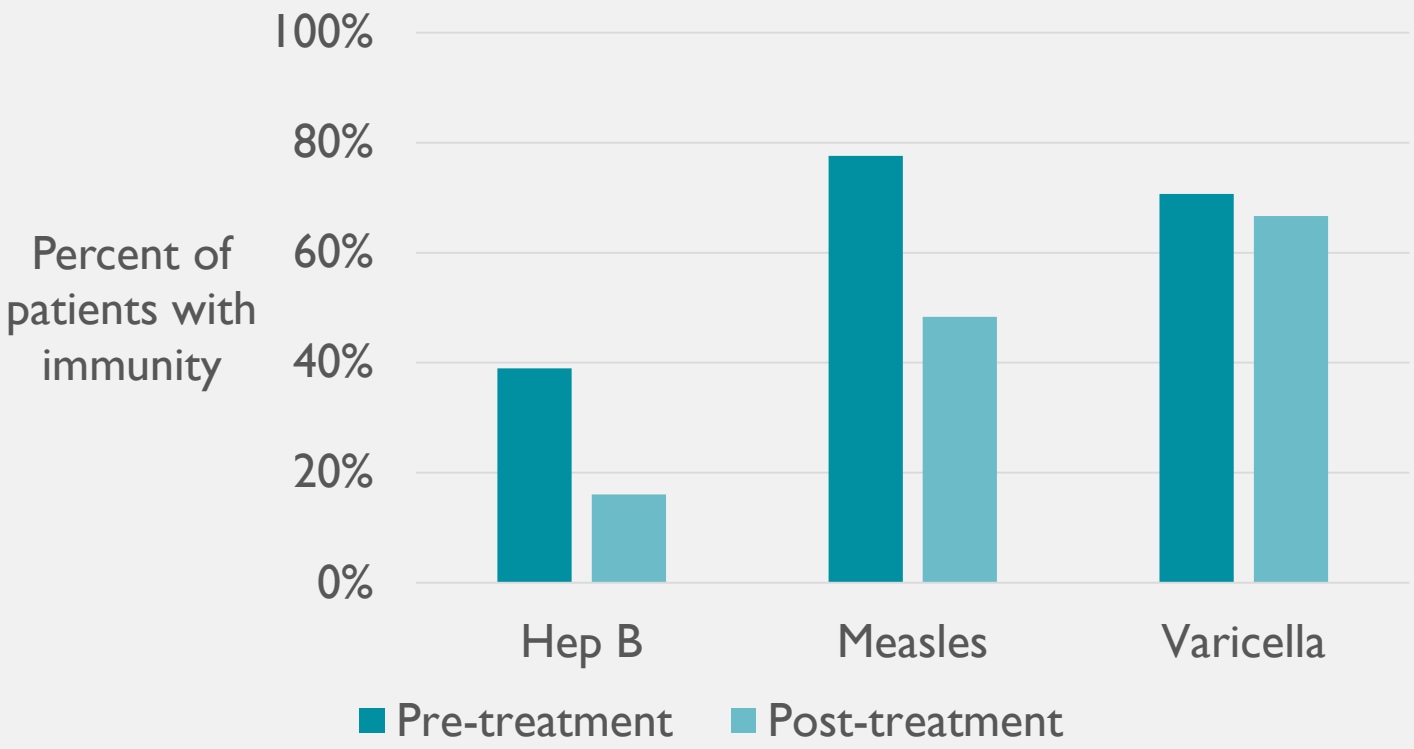
GP records of immunisation were compared with NIR data

Percentage of vaccines given found on NIR:



*NIR was established in 2005

Aim 4: Relationship between serology at diagnosis and 4-6 months post treatment.



Comparison with Auckland Results

	Christchurch	Auckland*
Study population	62	68
Patients avoiding at least one vaccine	69%	82%
No. of vaccines avoided	2.08	2.78
Average vaccines reduced	14 → 12	13 → 11
Cost benefit analysis	Costs > Savings	Pending
Time from EOT to serology	172 days	141 days
Time from serology to first vaccine	69 days	74 days

*Analysis conducted by Joyce Chan, ADHB

National Data – Preliminary

	Christchurch	Auckland*	National†
Study population	62	68	130
Patients avoiding at least one vaccine	69%	82%	76%
No. of vaccines avoided	2.08	2.78	2.45
Average vaccines reduced	14 → 12	13 → 11	13.5 → 11.5
Cost benefit analysis	Costs > Savings	Pending	Pending
Time from EOT to serology	172 days	141 days	156 days
Time from serology to first vaccine	69 days	74 days	72 days

*Analysis conducted by Joyce Chan, ADHB
†Preliminary analysis – awaiting full dataset

Benefits vs Costs of Serology

Benefits:

- Slight reduction in average number of vaccines given (14 → 12)

Costs:

- Extra blood test (+1 needle)
- Serology lab costs outweigh vaccine savings
- Introduces time delay and error individualising protocol

What next?

- Publish with combined Christchurch and Auckland data
- Meeting to determine plan for immunisation schedule has happened.
  - Re-immunisation schedule will revert to **immunising with all vaccines, no serology**.
  - Revised schedule currently being drafted
  - Considering testing varicella only – probable benefit for this vaccine and will not cause delays as given later in schedule.

Acknowledgements

Project Team:

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NCCN immunisation subgroup

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- Elizabeth Wilson (Starship ID Specialist)
- Diane Bos (Pegasus GP Group Immunisation Coordinator)
- Siobhan Cross (CHOC Paediatric Haematologist)
- Rob Corbett (CHOC Paediatric Oncologist)
- Tony Walls (Christchurch ID Specialist)
- Melissa Wilson (NCCN Administrator)

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