

B PART OF IT STUDY

Impact of 4CMenB on carriage of *Neisseria meningitidis* in adolescents

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37TH ANNUAL MEETING OF THE
**EUROPEAN SOCIETY FOR
PAEDIATRIC INFECTIOUS
DISEASES**

Organised jointly by ESPID and the ESPID foundation

LJUBLJANA
SLOVENIA
6-11 MAY,
2019

Speaker Disclosure

<i>Company Name</i>	<i>Honoraria/ Expenses</i>	<i>Consulting/ Advisory Board</i>	<i>Funded Research</i>	<i>Royalties/ Patent</i>	<i>Stock Options</i>	<i>Ownership/ Equity Position</i>	<i>Employee</i>	<i>Other (please specify)</i>
GlaxoSmithKline			X					



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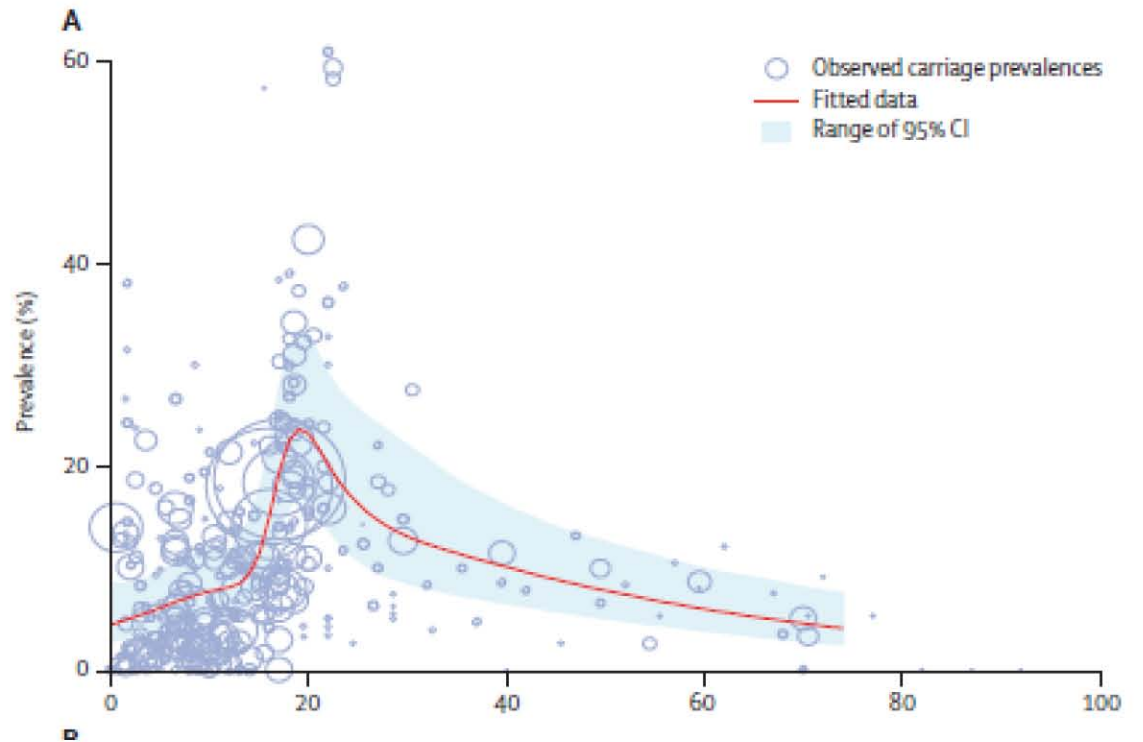
Health
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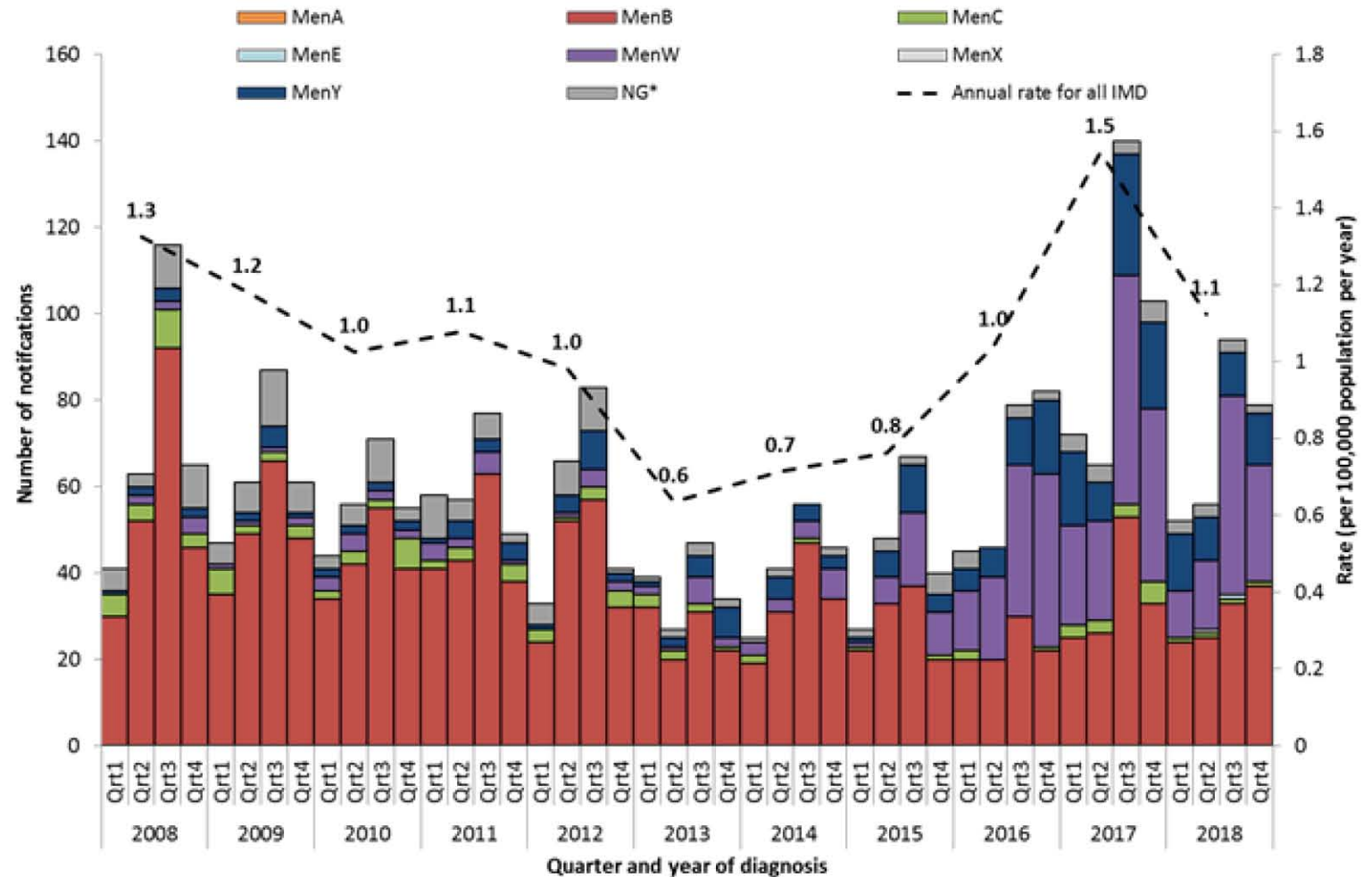
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Meningococcal disease

- Caused by different meningococcal serogroups A,B,C,W,X,Y
- Bimodal pattern of disease
 - Children < 5 years of age
 - Adolescents, 15-24 years of age
- Carriage
 - 10-20% of the population carry the meningococcus in their throat
 - Highest carriage rates are in adolescents



Changing epidemiology of meningococcal disease in Australia



Meningococcal vaccine programs in Australia

MenACWY vaccine (funded on the NIP)

- one dose, 12 months of age, from 01 July 2018
- one dose, 14-19 years of age from 01 April 2019

Meningococcal B vaccine

- Not included on the NIP in Australia
 - unfavourable cost effectiveness with uncertainties about effectiveness in a population program and impact on meningococcal carriage

84% effective against meningococcal B disease in infant program in UK ¹

Vaccine impact on meningococcal carriage?

- South Australian MenB vaccine program for infants, children, adolescents and young adults

Meningococcal disease in South Australia (SA)

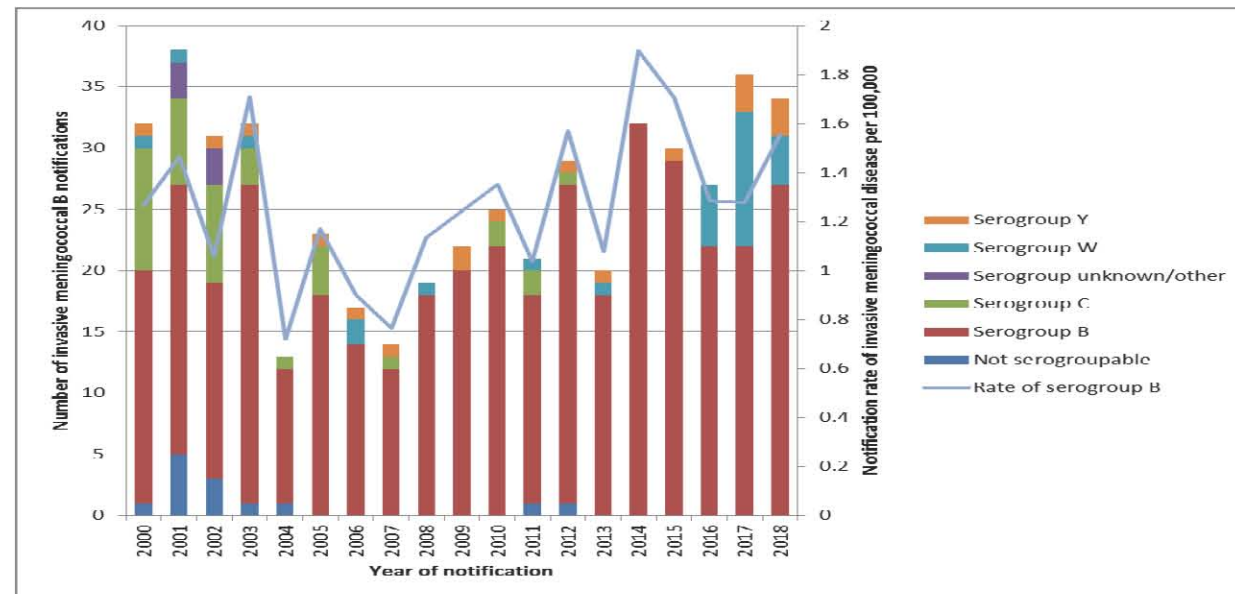
SA highest IMD notification rate in Australia
2.2/100,000

> 80% cases due to group B

Increasing rate of IMD due to group B in adolescents in SA

- ~75% of B cases are due to the hypervirulent New Zealand strain (CC 41/44)
- Vaccine coverage of strains will be ~ 90% as predicted by MATS testing

No ACWY or MenB vaccine program prior to or during the study period



1. National Notifiable Disease Surveillance http://www9.health.gov.au/cda/source/rpt_4.cfm
2. Lahra M et al. CDI 2016;40(4):E503-511

The study aim

To assess whether 4CMenB vaccine impacts on carriage of *Neisseria meningitidis* genogroups associated with invasive disease in adolescents.



Objectives

Primary Objective

- Estimate difference in carriage of disease causing genogroups of *N. meningitidis* (A, B, C, W, X, Y) in senior school students who received 4CMenB, compared to unvaccinated students.

Secondary objectives

- Estimate the difference in carriage of all and individual genogroups *N. meningitidis* in vaccinated vs unvaccinated students.
- Estimate the difference in acquisition of carriage of *N. meningitidis* in vaccinated vs unvaccinated students
- Identify risk factors associated with carriage in SA school students




B Part of It study

- Study design: Cluster RCT
 - Schools randomised to vaccine (2017) or control (vaccine in 2018)
- Setting: All schools in South Australia - metropolitan, rural, remote
- Population: Enrol senior (year 10, 11,12) students over 3 months (April-June 2017)
- Study processes:
 - 4CMenB vaccine (2 doses)
 - Oropharyngeal throat swabs at 0 and 12 months
 - Risk factor questionnaire

Risk factor questionnaire (based on UKMenCar4 study questionnaire)

- Sex
- Smoking
- Overcrowding – household size
- Antibiotic use
- Intimate kissing
- No. of partners
- No. nights out in preceding week
- Ethnicity



University Student Questionnaire

Please place identification sticker here

**** This information is completely confidential. Please answer the questions truthfully.****

Today's date (DD/MM/YYYY): / /

What is your residential postcode?

Name of University:

Please **colour in** the appropriate boxes e.g. ☐ or insert a number as required.

- I identify my sex as:

☐ Female
 ☐ Male
 ☐ Other
 ☐ Rather not say
- Have you ever received a Meningococcal B (Men B) vaccine?

☐ Yes
 ☐ No

If YES, can you please let us know the clinic where you received the vaccine so we can confirm the date of vaccination?
- Do you currently have a cold or sore throat?

☐ Yes
 ☐ No
- Are you currently taking or have you recently stopped taking antibiotics?

☐ Not taken in the past month
 ☐ Stopped in the last week
 ☐ Stopped in the last month
 ☐ YES, currently taking
- How many cigarettes do you smoke in a typical day?

☐ Don't smoke
 OR
 Number of cigarettes (enter the number in the boxes)
- How many times have you smoked an e-cigarette in the last week?

☐ Don't smoke
 OR
 Number of times
- How many times have you smoked a waterpipe (eg shisha) in the last month?

☐ Don't smoke
 OR
 Number of times
- Does any other person at home smoke cigarettes?

☐ Yes, outside the house
 ☐ Yes, inside the house
 ☐ No
- How many days in the last week have you been to a party, pub, bar or nightclub?

☐ 0
 ☐ 1
 ☐ 2
 ☐ 3
 ☐ 4
 ☐ 5
 ☐ 6
 ☐ 7 days
- How many people have you kissed (kissing with tongues, not just lips or cheeks) in the last week?

Number of people
- Are you currently in a relationship?

☐ Yes
 ☐ No


If YES, do they smoke cigarettes? ☐ Yes ☐ No
- Including yourself how many people live where you currently reside?

Number of people
- How many bedrooms are there where you currently live?



Number of bedrooms
- What ethnic group do you identify with?

☐ Aboriginal
 ☐ Torres Strait Islander
 ☐ Caucasian
 ☐ Asian
 ☐ Middle East
 ☐ African
 ☐ Pacific Islander
 ☐ Other

Thank you for completing this questionnaire.

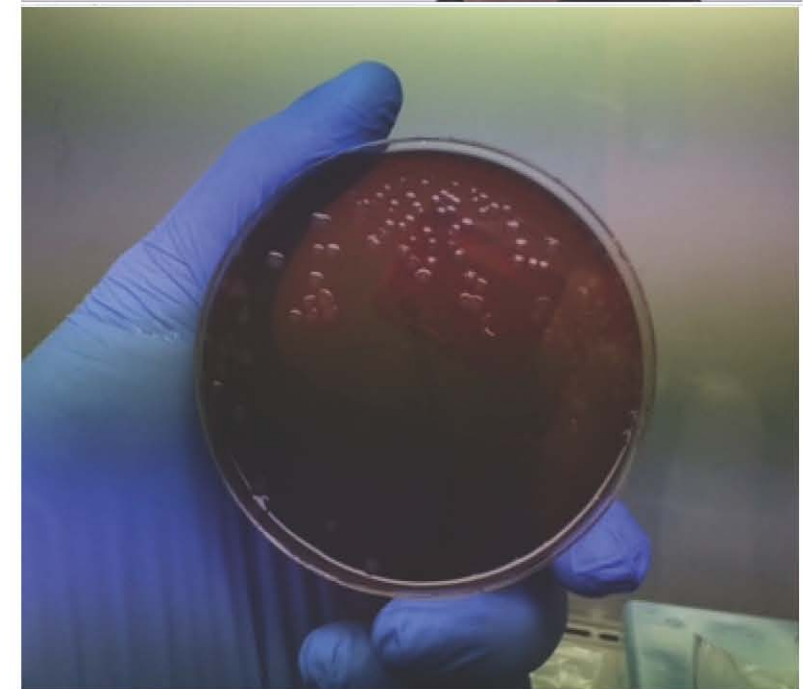
please turn over 

Questionnaire - University Students V5, 16 Dec 2016

Laboratory methods

- Oropharyngeal swabs collected on day 1 and 12 months
- Swab placed in liquid transport medium (STGG)
- Real time PCR (porA NAT analysis)
- Meningococcal genotyping
- Culture for *Neisseria* on selective agar
- Isolates underwent whole genome sequencing



Communication



A social media strategy encompassing all major platforms



More than 2.69 million impressions on Facebook



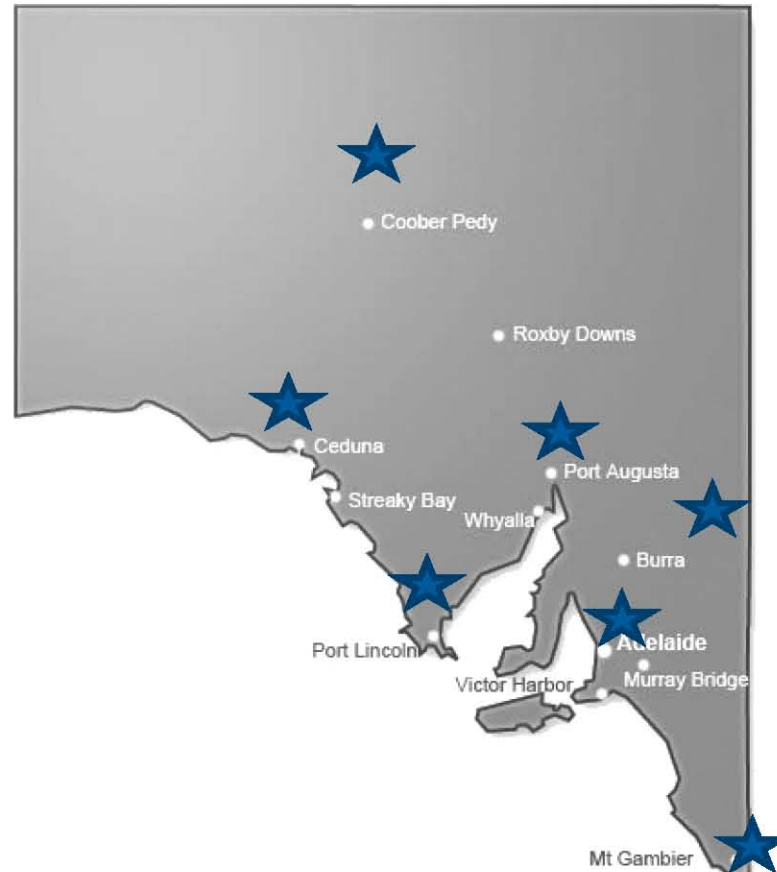
Our commercial gained more than 1,200 metro TV placements



More than 45 pieces of local content, featuring teachers, students, survivors of Men B, ambassadors, online influencers and parents were developed.



Training in study processes, good clinical practice and throat swab technique, transport of samples from rural and remote communities



4,990 kms
travelled in
Adelaide and
country
centres

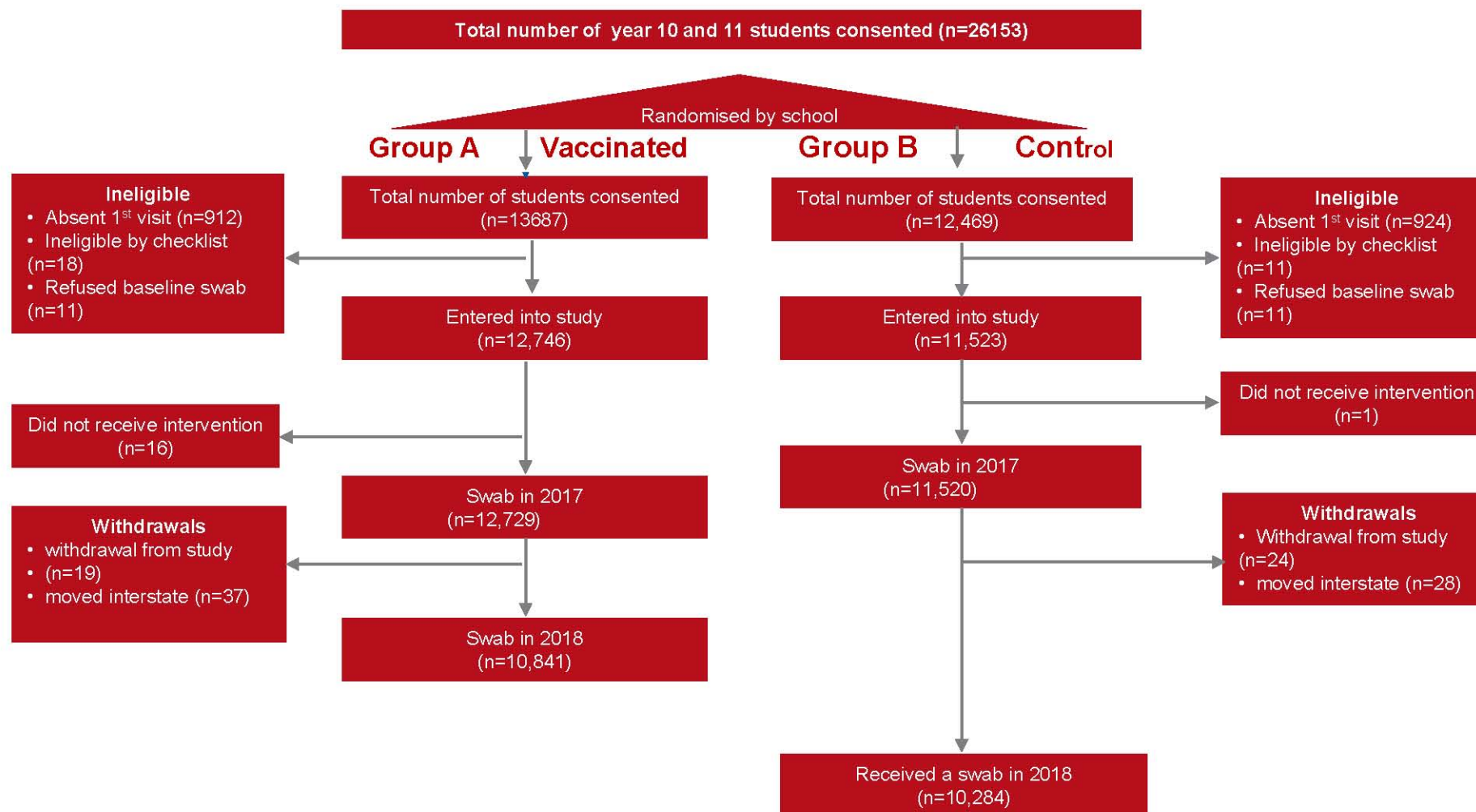


Trained
• >250 nurses
• 35 admin staff

Results



Participant flow students



238 schools
(>95% of SA schools)

Total enrolment
34,489 students
(62%)

Intervention

- **99.5%** of students received 1 dose of 4CMenB

- **97%** of students received 2 doses 4CMenB

88.4% completion

Baseline characteristics of vaccinated and unvaccinated students

Characteristic	Vaccinated (%)	Unvaccinated (%)
Age (mean)	15.6	15.6
Gender		
• Female	6670 (52.3)	5795 (50.3)
Ethnicity		
• Aboriginal	361 (2.9)	290 (2.6)
• Caucasian	9089 (72.4)	7964 (70.2)
• Asian	1216 (9.7)	1173 (10.3)
Smoker		
• Cigarettes	208 (1.6)	181 (1.6)
• Waterpipe	369 (2.9)	281 (2.5)
• E-cigarette	127 (1.0)	127 (1.1)
School location		
• Metropolitan	9829 (77.1)	8147 (70.7)
• Rural	2917 (22.9)	3376 (29.3)
Year of schooling		
• Year 10	6576 (51.6)	6188 (53.7)
• Year 11	6170 (48.4)	5335 (46.3)
Boarding student	340 (2.7)	190 (1.7)

No significance difference between groups for any characteristic

***N. Meningitidis* carriage prevalence at baseline and 12 months**

Carriage Prevalence	2017 Baseline Vaccinated %	2017 Baseline Control %	2018 12 months vaccinated %	2018 12 month control %
<i>All N. meningitidis</i>	2.80	2.62	4.00	4.66
<i>Invasive N. meningitidis</i>	1.33	1.42	2.35	2.43
Genogroup B	0.83	0.72	1.14	1.11
Genogroup C	0.02	0.06	0.11	0.07
Genogroup W	0.07	0.10	0.16	0.18
Genogroup Y	0.41	0.55	0.88	1.10

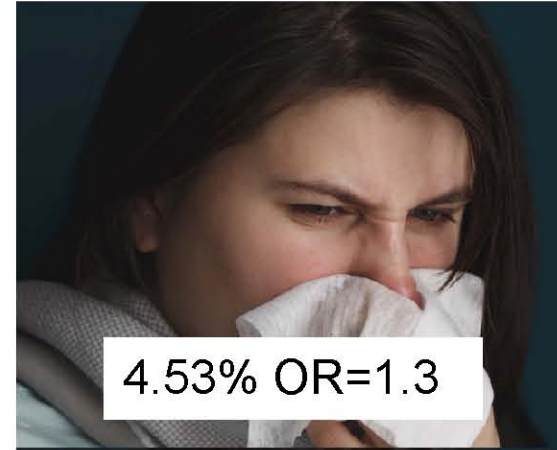
4CMenB impact on *N. meningitidis* carriage

Intention to treat analysis (According To Protocol same result)

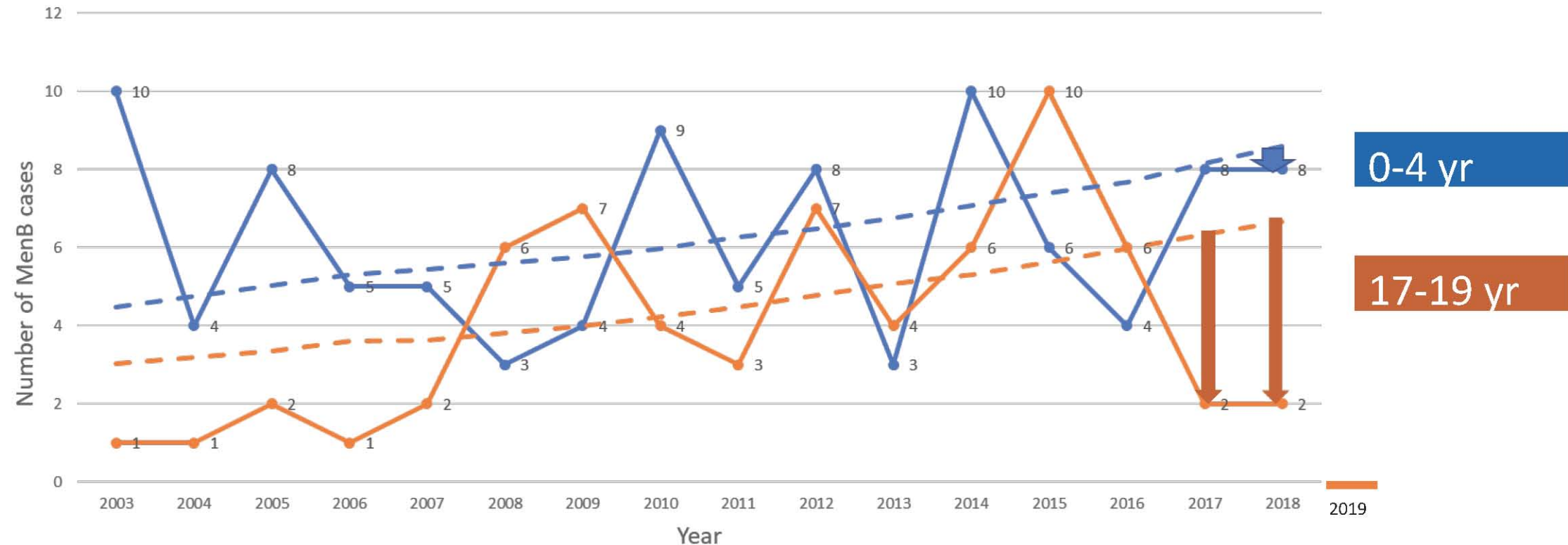
<i>N. meningitidis</i>	vaccinated		unvaccinated		aOR (95% CI)	ap-value
All	4.3 %	547/12746	4.9%	561/11523	0.85 (0.70, 1.04)	0.117
Disease causing (ABCWYX)	2.6%	326/12746	2.5%	291/11523	1.02 (0.8, 1.31)	0.845
Post hoc analysis	Vaccinated		Control		Adjusted Odds ratio 95% CI	Adjusted p-value
	%	n	%	n		
Non-typeable	1.65	179/10841	2.23	229/10285	0.71 (0.54, 0.91)	0.008
Genogroup W	0.16%	17/10841	0.18%	18/10285	0.89 (0.43, 1.85)	0.751
Genogroup C	0.11%	12/10841	0.07%	7/10285	1.87 (0.63, 5.55)	0.260
Genogroup X	0.07%	8/10841	0.01%	1/10285	-	-
<i>Acquisition N. meningitidis</i>	vaccinated		unvaccinated		aOR (95% CI)	ap-value
All genogroups	3.2 %	353/10937	3.6%	373/10342	0.89 (0.71, 1.11)	0.298
Disease causing genogroups	2.0%	219/10888	2.0%	208/10315	0.99 (0.76, 1.30)	0.954

Generalised estimating equation: Adjusted for school size, school SES (ICSEA), baseline carriage of *N. meningitidis*

Independent risk factors for carriage of *N. meningitidis*



Exploratory Aim: Impact of 4CMenB vaccine on IMD; observed vs expected MenB cases



No cases in 15-24
yr olds 2019 to date

Vaccine safety (n=58,168 doses)

- Independent vaccine safety committee
- Total 192 AEFIs reported (0.34% 192/56,500)
- 69 medically attended events, 9 SAEs
- Special Immunisation Service clinic review for any unusual events eg rashes, immunisation related stress disorder
- No safety concerns or safety signals detected

Unintended consequences

- Parents who have never previously vaccinated their children enrolled them in the “B Part of It” study and their children received their first ever vaccine
- Facilitated adolescent engagement in health decisions, improved health literacy and education in relation to meningococcal disease, provided a research experience for school students
- “B Part of It” became one of the most popular year 12 student research projects in SA for 2017
- Improvements in the school immunisation program eg use of SMS reminders to students
- Ensuring equity in access to vaccines and follow-up eg students in juvenile detention

Summary

4CMenB vaccine is safe and effective in preventing meningococcal disease in the largest cohort of adolescents vaccinated worldwide

4CMenB vaccine did not show prevention of acquisition of carriage of genotypes associated with disease (A,B,C,W,Y) *

MenB vaccine programs should be designed to provide DIRECT protection for those at highest risk of disease

Exploratory objectives

- Does 4CMenB vaccine prevent carriage of the hypervirulent strain causing disease ?
- Does 4CMenB vaccine impact on density of the meningococcus being carried?

Further research

- Impact of 4CMenB on Neisseria gonorrhoea disease ¹



Vaccine impact on hypervirulent genotypes associated with disease

More will be revealed
Friday 10.30-10.40
Kocka Hall

Vaccine impact on hypervirulent strains
clonal complex MLST

Clonal complex	MLST	Vaccinated N	%	p-value	aOR 95%CI ~	ap-value	
B 41/44	6058			0.08	0.50 (0.18, 1.42)	0.19	
		0	0.00	0.13*			
		0	0.06	7 0.07			0.71
Y 167	1624	4	0.04	18 0.18	0.002	0.20 (0.06, 0.59)	0.004



Vaccine impact on carriage density

Outcome	Vaccinated n (%)	Unvaccinated n (%)	Odds Ratio (95% CI)	P
All carriage	275 (77)	197 (65)	1.85 (1.31 to 2.61)	0.0004
Disease-causing	125 (74)	115 (65)	1.55 (1.02 to 2.35)	0.036
- Genogroup B	78 (72)	68 (63)	1.66 (0.85 to 3.25)	0.18
- Genogroup C	47 (43)	47 (43)	1.55 (0.02 to 7.22)	0.48
- Genogroup D	150 (80)	88 (68)	1.66 (0.26 to 33.97)	0.38
- Genogroup E	150 (80)	88 (68)	1.15 (0.55 to 2.39)	0.71
N	150 (80)	88 (63)	2.35 (1.31 to 4.21)	0.004

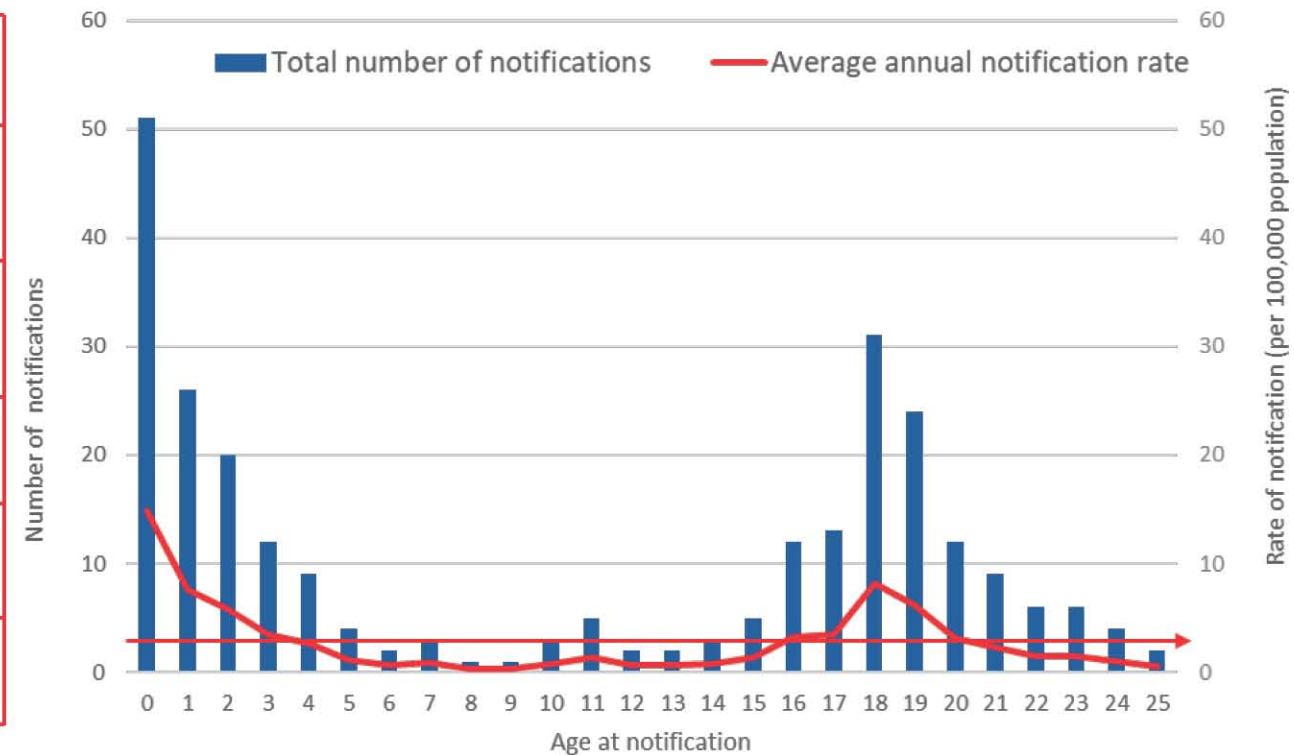
Increased carriage clearance in vaccinated compared to unvaccinated

More will be revealed
Friday 11.10-11.20
Kocka Hall

4CMen B vaccine program in South Australia for infants, children, adolescents and young people

Direct protection for age groups at highest risk of disease

Age	Program	Start date
6 weeks - 12 months	Infants	1 October 2018
12 months -<4 years	Childhood catch-up	1 October 2018
15 and 16 years	Adolescents	1 February 2019
16 and 17 years	Adolescent catch-up	1 February 2019
17 - <21 years	Young Adult catch-up	1 February 2019



B Part of It Team

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Ms Luda Molchanoff, Country Health
Mrs Ann Marie Hayes, DECS
Mrs Monica Conway, CESA
Ms Carolyn Grantskaln, Bronwyn Donaghey, AIS
Ms Sarah Scott, University of Adelaide
Ms Lynette Kelly, University of Adelaide
Council CEOs, immunisation coordinators and nurses
VIRTU team



Reference group

Professor Don Robertson (Chair), Emeritus Professor, The University of Adelaide
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Mr Bishop Rizkalla, Vaccines Medical Director, GSK

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- Professor Adam Finn, Professor of Paediatrics and President ESPID, University of Bristol
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