Effectiveness and impact of the 4CMenB vaccine against invasive serogroup B meningococcal disease and gonorrhoea in an infant, child, and adolescent programme: an observational cohort and case-control study

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Summary

Background A programme of vaccination with the four-component serogroup B meningococcal (4CMenB) vaccine was introduced in South Australia for infants and children aged 0–3 years on Oct 1, 2018, and for senior school students in school years 10 and 11 (aged 15–16 years) and young adults aged 17–20 years on Feb 1, 2019. We aimed to evaluate vaccine effectiveness and impact on serogroup B meningococcal disease and gonorrhoea 2 years after implementation of the programme.

Methods We did a cohort and case-control study among those targeted by the South Australia 4CMenB vaccination programme. We obtained disease notification data from SA Health, Government of South Australia, and vaccine coverage data from the South Australian records of the Australian Immunisation Register. Vaccine effectiveness was estimated as the reduction in the odds of infection using the screening and case-control methods. Vaccine impact was estimated as incidence rate ratios (IRRs), obtained by comparing case numbers in each year following the start of the vaccination programme with cases in the equivalent age cohort during the pre-vaccination programme years. We used Poisson or negative binomial models, as appropriate, with adjustment for changes in the incidence of serogroup B meningococcal disease in age cohorts not eligible for vaccination through the state programme.

Findings 4CMenB vaccine coverage 2 years after introduction of the childhood vaccination programme was 94·9% (33 357 of 35 144 eligible individuals) for one dose, 91·4% (26 443 of 28 922) for two doses, and 79·4% (15 440 of 19 436) for three doses in infants. The one-dose (77·1%, 16 422 of 21 305) and two-dose (69·0%, 14 704 of 21 305) coverage was highest in adolescents born in 2003 (approximately year 10 students). 2 years after implementation of the childhood vaccination programme, incidence of serogroup B meningococcal disease was significantly reduced compared with before programme implementation in infants aged 12 weeks to 11 months (adjusted IRR [aIRR] 0·40 [95% CI 0·23–0·69], p=0·0011), but not in those aged 1 year (0·79 [0·16–3·87], p=0·77), 2 years (0·75 [0·18–3·14], p=0·70), or 4 years (3·00 [0·47–18·79], p=0·24). aIRRs were not calculable in those aged 3 or 5 years because of no cases occurring after programme implementation. aIRR for serogroup B meningococcal disease was 0·27 (0·06–1·16, p=0·078) in adolescents aged 15–18 years 2 years after implementation of the adolescent and young adult programme, and 1·20 (0·70–2·06, p=0·51) in those aged 19–21 years in the first year. Two-dose vaccine effectiveness against serogroup B meningococcal disease was estimated to be 94·2% (95% CI 36·6–99·5) using the screening method and 94·7% (40·3–99·5) using the case-control method in children, and 100% in adolescents and young adults (no cases reported after implementation). Estimated two-dose vaccine effectiveness against gonorrhoea in adolescents and young adults was 32·7% (8·3–50·6) based on the case-control method using age-matched individuals with chlamydia infection as controls.

Interpretation 4CMenB vaccine shows sustained effectiveness against serogroup B meningococcal disease 2 years after introduction in infants and adolescents, and moderate effectiveness against gonorrhoea in adolescents. The high vaccine effectiveness against serogroup B meningococcal disease is likely due to high coverage in the target age groups and close antigenic match between the 4CMenB vaccine and the disease-associated serogroup B meningococcal strains circulating in South Australia. COVID-19-related physical distancing policies might have contributed to further declines in serogroup B meningococcal disease cases during the programme's second year.

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Introduction

Although uncommon, invasive meningococcal disease causes death in young children and adolescents in 5–10% of cases.[1] Invasive meningococcal disease incidence peaks in children younger than 5 years with a second peak in adolescents and young adults aged

Research in context

Evidence before this study

We searched PubMed using the following terms: "meningococcal serogroup B vaccine", "4CMenB", "Bexsero", and any combination of "vaccine effectiveness" or "impact". Languages were not limited. The search was limited to articles published after 2015, as the first publicly funded four-component serogroup B meningococcal (4CMenB) vaccine programme commenced in 2015 in the UK. Reference lists of relevant review articles were also checked to supplement our searching. The effectiveness and impact of the 4CMenB vaccine against invasive meningococcal disease have been reported in the UK, Canada, Italy, and Portugal for infants, and in Canada and South Australia for adolescents. Reductions in the incidence of serogroup B meningococcal disease ranged from 31% to 96%, with age groups, follow-up periods, and analyses varying across studies. Vaccine effectiveness against serogroup B meningococcal disease ranged from 50% to 100%, dependent on the method of estimation used (eg, screening method, case-control method, and Poisson regression) in studies. Recent evidence of cross-protection of 4CMenB against gonorrhoea comes from a case-control study in New Zealand, showing that the outer membrane vesicle (OMV) vaccine (MeNZB) introduced in 2004 was associated with reduced risk of gonorrhoea in people aged 15–30 years. Using people diagnosed with chlamydia as controls, vaccine effectiveness against gonorrhoea in New Zealand was estimated at 31% (95% CI 21 to 39). The mass vaccination campaign in Canada, using the 4CMenB vaccine, also showed a potential effect on gonorrhoea. The estimate of vaccination impact was a risk reduction in gonorrhoea of 59% (–22 to 84). A US case-control study found that the 4CMenB vaccine was associated with a lower risk of gonococcal infection, with estimated vaccine effectiveness of 36% (23 to 52). However, 4CMenB was only offered to adolescents and young adults in outbreak control programmes over a short period. Ongoing serogroup B meningococcal disease vaccine programmes have not previously been implemented in both adolescents and young children.

Added value of this study

The serogroup B meningococcal disease vaccination programme implemented in South Australia is the only large expansive programme globally funding Bexsero for ten age cohorts, including three catch-up cohorts and two ongoing cohorts in infants, young children, adolescents, and young adults. The programme will continue indefinitely after showing effectiveness at preventing serogroup B meningococcal disease in high-risk age groups. Using data from national registers, we estimated both vaccine impact against serogroup B meningococcal disease and gonorrhoea, as well as vaccine effectiveness using both the screening and case-control methods. These results provided real-world evidence that 4CMenB vaccine is highly effective in preventing serogroup B meningococcal disease in infants and adolescents, as well as providing moderate cross-protection against gonorrhoea.

Implications of all the available evidence

Given the significance and precedence of this programme in both the Australian and global context, ongoing evaluation of the state programme is essential to demonstrate not only the programme's effectiveness, but, more importantly, to inform public health policy and build immunisation provider and public trust in future programmes. The vaccine impact on gonorrhoea in addition to meningococcal disease will be important for measuring the cost-effectiveness of the future 4CMenB vaccination programmes. Targeted increased access and messaging to improve uptake in Aboriginal and Torres Strait Islander young people should be implemented.

15–24 years.[2] The majority of cases of invasive meningococcal disease in Europe, Australia, New Zealand, and much of the Americas are caused by *Neisseria meningitidis* (meningococcus) serogroup B bacteria.[3] In South Australia, most cases of serogroup B meningococcal disease over the past few decades have been caused by the New Zealand epidemic strain clonal complex (cc) 41/45: PorA 1.7,2.4.[3] In 2018, the South Australia Government implemented a 3-year programme of vaccination against serogroup B meningococcal disease with the four-component serogroup B meningococcal (4CMenB) vaccine Bexsero (manufactured by GlaxoSmithKline), targeting the highest-risk populations.[4] In October, 2018, the 4CMenB vaccine was offered to all infants younger than 12 months, to be administered at age 6 weeks, 4 months, and 12 months or with a minimal interval of 2 months between doses (table 1). Two-dose childhood catch-up vaccination was offered to children aged 1–3 years. In 2019, students in school years 10 and 11 (15–17 years of age) were offered two-dose vaccination through a school-based immunisation programme with an ongoing school-based programme for year 10 students. A catch-up programme was also available for those aged 17–20 years between February, 2019, and February, 2020.

Several 4CMenB childhood and adolescent programme evaluations have shown good effectiveness against serogroup B meningococcal disease.[5–10] Emerging evidence has also suggested that meningococcal group B outer membrane vesicle (OMV) vaccines, including 4CMenB, might offer some protection against gonorrhoea, which is caused by *Neisseria gonorrhoeae* (gonococcus) bacteria.[11,12] The health impacts of gonorrhoea are greatest for women, as gonorrhoea is an important cause of pelvic inflammatory disease resulting in infertility. In 2016, the global prevalence of gonorrhoea was 0·9% in women and 0·7% in men, with 86·9 million total estimated incident cases among people aged

15–49 years.[13] WHO considers gonorrhoea a major public health problem requiring urgent solutions because of increasing antimicrobial resistance to extended-spectrum cephalosporins, the only first-line antimicrobial therapy for gonorrhoea.[14] Proteins targeted by 4CMenB are present not only in *N meningitidis* but also *N gonorrhoeae*, with very high sequence similarity of outer membrane proteins within *N meningitidis* serogroup B and *N gonorrhoeae* (mean sequence similarity 91·0% [SD 9·8%]).[15]

South Australia is the first place globally to implement an extensive 4CMenB programme targeting infants, young children, adolescents, and young adults, for ten age level cohorts (those aged <1 year, 1–3 years, and 15–20 years), providing a unique opportunity to evaluate the effectiveness of the vaccine against serogroup B meningococcal disease and gonorrhoea. A publicly funded programme of vaccination against serogroup B meningococcal disease has never been offered to infants and adolescents concurrently. In this Article, we report the vaccine impact and effectiveness of 4CMenB against serogroup B meningococcal disease and gonorrhoea after the programme's first 2 years.

Methods

Study design

We did a cohort and case-control study among children, adolescents, and young adults targeted by the South Australia 4CMenB vaccination programme. Vaccine impact was measured using an interrupted-time-series design comparing pre-vaccination and vaccination periods in child and adolescent cohorts. Vaccine effectiveness was estimated using screening method and case-control methods. The study protocol was previously published.[16]

The study was approved by South Australia Department for Health and Wellbeing Human Research Ethics Committee (HREC/19/SAH/59). The study followed the STROBE guidelines.[17]

Data sources

Serogroup B meningococcal disease and gonorrhoea notification data were provided by the Communicable Disease Control Branch (CDCB) of SA Health, Government of South Australia. Socioeconomic status was estimated using the Socio-Economic Index for Areas (SEIFA) Index of Relative Socio-economic Disadvantage (IRSD) based on postcode of residence.[18] Socioeconomic status was categorised into three groups: low (1–4), medium (5–7), and high (8–10) using SEIFA IRSD national decile scores. Vaccine coverage was calculated on the basis of South Australian records provided from the Australian Immunisation Register. The serogroup B meningococcal disease vaccine records were extracted from the South Australian records from the Australian Immunisation Register on Jan 13, 2021, for children born on or after Oct 1, 2014; and on March 29, 2021, for adolescents and young adults born between Feb 1, 1998, and Jan 1, 2007.

Data on age, sex, Aboriginal status, and postcode of residence were extracted from the South Australian records of the Australian Immunisation Register. Access to the South Australian records of the Australian Immunisation Register was approved by the Data Release Team, Australian Government Department of Health. All data extracted from these records were password protected and de-identified for analysis and case-control matching. The multivariable logistic regression models were used to assess sociodemographic factors associated with vaccine coverage. The model was adjusted for potential confounding variables including age, Aboriginal and Torres Strait Islander status, socioeconomic status, and sex. If up to 1% of people had missing values for a specific variable, those people with missing information were excluded from the analysis. If more than 1% of people had missing values for a variable of interest, an additional category of "unknown" was created to retain those with missing data. For the childhood vaccination programme, vaccine-eligible cohorts were categorised based on the vaccination programme year starting on Oct 1 and ending the next year on Sept 30, because vaccine eligibility was defined as birth on or after Oct 1, 2014. For the adolescent vaccination programme, age groups were categorised based on the calendar year, as most serogroup B meningococcal vaccines were given to students in school years 10 and 11 (approximate birth cohort 2002–04) through the school immunisation programme based on their school years.

Estimation of vaccine impact

Vaccine impact was calculated by comparing the incidence of serogroup B meningococcal disease in the years before the 4CMenB vaccination programme with that in the complete programme years after the state vaccine programme commenced (October to the

	Age group targeted	Number of doses	Programme start date	Programme end date
Childhood programmes				
Ongoing childhood programme	≤12 months	Two primary doses and one booster dose	Oct 1, 2018	Ongoing
Catch-up childhood programme	>12 months to <4 years	Two doses	Oct 1, 2018	Dec 31, 2019
Adolescent and young adult programmes				
Ongoing adolescent (year 10) school-based programme	~15 to 16 years	Two doses	Feb 1, 2019	Ongoing
Catch-up adolescent (year 11) school-based programme	~16 to 17 years	Two doses	Feb 1, 2019	Dec 31, 2019
Catch-up young adult programme	17 to <21 years	Two doses	Feb 1, 2019	Feb 29, 2020

Table 1: **Summary of the South Australia serogroup B meningococcal immunisation programme**

following September for the childhood programmes, and February to the following January for the adolescent and young adult programmes).

To calculate vaccine impact in each vaccine-eligible group, incidence rate ratios (IRRs) were estimated by comparing case numbers in each year following the start of the vaccination programme with cases in the equivalent age cohort during the pre-vaccination programme years (October, 2012, to September, 2018, for the childhood programme, and February, 2011, to January, 2019, for the adolescent and young adult programme). To consider any changes over time unrelated to 4CMenB vaccination, IRRs were adjusted to account for changes in the incidence of serogroup B meningococcal disease or gonorrhoea in age cohorts of the population who were not in the vaccine-eligible cohorts. To obtain the adjusted IRRs (aIRRs), a Poisson regression model was applied to evaluate vaccine impact on serogroup B meningococcal disease. Because of overdispersion in the Poisson regression model in estimation of vaccine impact on gonorrhoea, a negative binomial regression model was instead fit. Population denominators were obtained from the Australian Bureau of Statistics[19] and used as offset terms in the statistical models. To estimate the expected number of cases, the model was fit without including data for vaccine-eligible cohorts, and predictions for the vaccine-eligible cohorts were subsequently derived from this model. Pearson's goodness-of-fit test was found to be satisfactory for each model. Results yielding a p value less than 0·05 were considered statistically significant.

Estimation of vaccine effectiveness

Vaccine effectiveness was estimated for vaccine-eligible cohorts under the routine programme with laboratory-confirmed serogroup B meningococcal disease. For estimates of vaccine effectiveness, a vaccine dose was considered valid if received at least 14 days before onset of serogroup B meningococcal disease.

Vaccine effectiveness against serogroup B meningococcal disease was assessed using two previously published methods: the screening[7,8] and case-control[20] methods. For serogroup B meningococcal disease cases, 20 controls matched by date of birth (±28 days) were randomly sampled for each case from the de-identified South Australian dataset. Logistic regression was used with vaccination status of the case as the binary outcome variable. Vaccine effectiveness was calculated as 1 minus the odds ratio (OR). CIs were calculated using the same formula.

See Online for appendix

In the estimation of vaccine effectiveness against gonorrhoea, patients with a diagnosis of chlamydia were chosen as controls to reduce the potential for confounding because of similar sexual behavioural risks reported in patients with gonorrhoea and chlamydia. In patients with repeat episodes, only the first recorded diagnosis was included in the analysis. This approach was previously used in a retrospective case-control study assessing vaccine effectiveness of a meningococcal group B OMV vaccine against gonorrhoea.[11] The chlamydia controls matched for date of birth (±28 days) were selected from the notification database. The screening method[7,8] and case-control method with 20 controls from the Australian Immunisation Register[20] were also explored. Gonorrhoea cases in the adolescent programme were included if they were eligible by age for the ongoing or catch-up adolescent or young adult programmes. Infection with gonorrhoea can be present months before diagnosis, and vaccine doses were therefore counted if disease onset occurred at least 6 months after the dose. All chlamydia controls matched to cases without replacement were included.

For our primary analysis, and to reflect real-world data, we included all gonorrhoea-positive cases who had or did not have chlamydia co-infection at the time of the first episode of gonorrhoea. Controls were chlamydia-positive only. Co-infections can affect the interpretation of studies about transmission, immune response, and, importantly, vaccine effect; therefore, we conducted sensitivity analyses to estimate gonorrhoea-only infection (excluding co-infected gonorrhoea cases). Results yielding a p value less than 0·05 were considered statistically significant.

Role of the funding source

The funder of the study was involved in study design, data collection, data interpretation, and writing of the report, but had no role in data analysis.

Results

For the analysis of vaccine coverage among children targeted by the childhood ongoing and catch-up programmes, all children born after June 30, 2020 (younger than 3 months on Sept 30, 2020), were excluded from the one-dose coverage analysis; children born after March 31, 2020 (younger than 6 months on Sept 30, 2020), were excluded from the two-dose analysis; and only children born between April 30, 2018, and June 30, 2019 (aged from 1 year and 3 months to 2 years and 5 months on Sept 30, 2020) were included in three-dose coverage analysis (figure 1; appendix pp 4–5). 4CMenB vaccine coverage in children 2 years after commencement of the childhood ongoing and catch-up programmes on Sept 30, 2020, was 94·9% (95% CI 94·7–95·1; 33 357 of 35 144 eligible individuals) for one dose, 91·4% (91·1–91·7; 26 443 of 28 922) for two doses, and 79·4% (78·9–80·0; 15 440 of 19 436) for three doses in children who were born after Oct 1, 2018, and eligible to receive one, two, or three doses.

Children born between April 1, 2018, and June 30, 2019, were included in the adjusted logistic regression analysis to investigate the demographic factors associated with three-dose vaccine uptake (appendix p 2). Receipt of three doses of 4CMenB vaccine was less likely in Aboriginal children versus non-Indigenous children (adjusted OR [aOR] 0·58 [95% CI 0·51–0·66]) and in 2-year-old versus 1-year-old children (0·62 [0·58–0·66]).

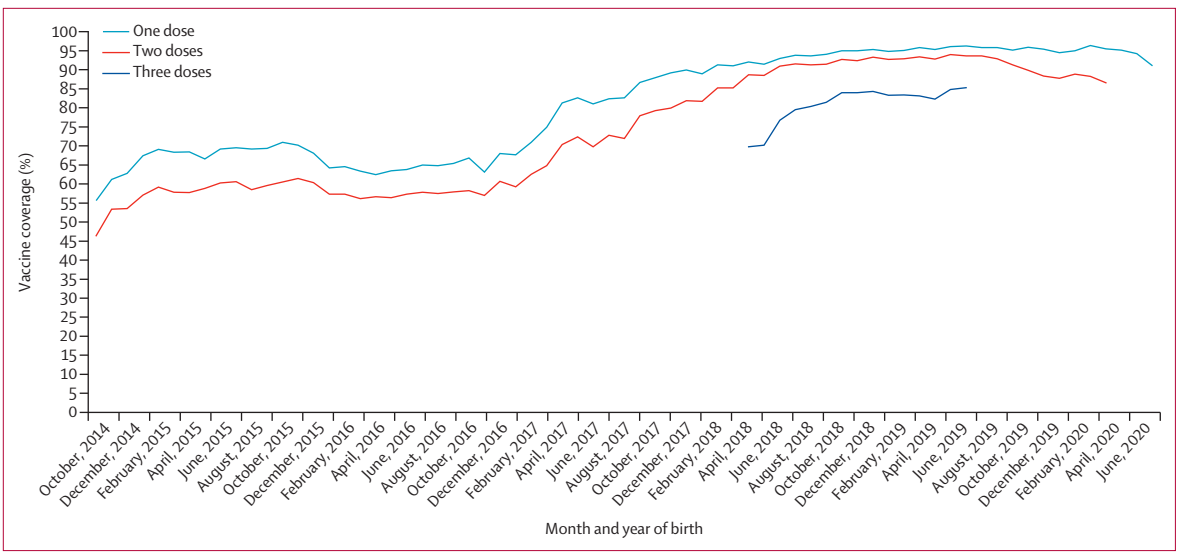

Figure 1: **Vaccine coverage for the ongoing and catch-up childhood vaccination programmes, by year and month of birth**
Vaccine coverage was calculated on the basis of Australian Immunisation Register data extracted on Jan 13, 2021. A minimum 3-month lag period was allowed for late notification of vaccinations to the Australian Immunisation Register. Therefore, the figure shows one-dose coverage for children born between Oct 31, 2014, and June 30, 2020; two-dose coverage for children born between Oct 31, 2014, and March 31, 2020; and three-dose coverage for infants born between April 30, 2018, and June 30, 2019.

During the 2 years after commencement of the adolescent and young adult vaccination programmes, 53 356 adolescents and young adults received at least one dose of 4CMenB. There were 46 083 adolescents and young adults who received the two-dose 4CMenB schedule. Adolescents born in 2003 (aged approximately 16 years as of January 31, 2020) had the highest rates of one-dose coverage (77·1% [95% CI 76·5–77·6]; 16 422 of 21 305 eligible individuals) and two-dose coverage (69·0% [68·4–69·6]; 14 704 of 21 305; figure 2; appendix pp 3, 6). Vaccine uptake was lower in those with low (aOR 0·63 [95% CI 0·61–0·65]) or medium socioeconomic status (0·75 [0·73–0·77]) versus high socioeconomic status, in Aboriginal and Torres Strait Islander individuals (0·33 [0·31–0·35]) and those with unknown Aboriginal status (0·18 [0·17–0·20]) versus non-Indigenous individuals, and in males (0·82 [0·80–0·84]) versus females (appendix p 2).

2 years after the implementation of the state 4CMenB childhood vaccination programme, a 60% reduction in the incidence of serogroup B meningococcal disease in infants aged 12 weeks to 11 months was observed (two observed cases *vs* 5·21 expected cases; aIRR 0·40 [95% CI 0·23–0·69]; table 2). The reductions among children aged 1 year (21%; 0·79 [0·16–3·87]) and 2 years (25%; 0·75 [0·18–3·14]) were modest and not statistically significant, with wide CIs. In each of the first year (October, 2018, to September, 2019) and second year (October, 2019, to September, 2020) of the state vaccination programme compared with the pre-vaccination period (appendix p 3), similar reductions in the incidence of serogroup B meningococcal disease in infants aged 12 weeks to 11 months were observed. Adjusted IRRs were not calculable for children in other age groups eligible to receive the state-funded free 4CMenB vaccine because there were no cases in these age groups.

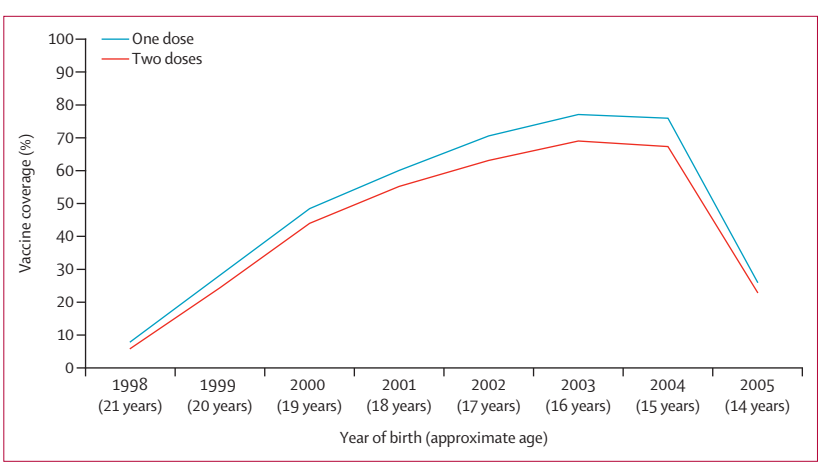

Figure 2: **Vaccine coverage for the ongoing and catch-up adolescent and young adult programmes, by year of birth**
Vaccine coverage was calculated on the basis of Australian Immunisation Register data extracted on March 29, 2021. The figure shows one-dose and two-dose coverage for adolescents and young adults between Jan 1, 1998, and Dec 31, 2005. The school year was not captured in the Australian Immunisation Register records and vaccine coverage is shown by age (birth year) for adolescents and young adults who might be eligible to receive the serogroup B meningococcal disease vaccine under the ongoing and catch-up programmes for adolescents and young adults.

2 years after commencement of the adolescent and young adult vaccination programme, a 73% reduction in the incidence of serogroup B meningococcal disease in adolescents aged 15–18 years was observed

	Pre-vaccination period		Vaccination period		IRR*	Vaccine-eligibility adjusted IRR†
	Annual mean number of cases	Annual incidence per 100 000 population	Annual mean number of cases	Annual incidence per 100 000 population		
0 to 11 weeks	0·00	0·00	0·50	11·39	..	..
12 weeks to 11 months	2·67	17·20	1·00	6·83	0·40 (0·27–0·59), p<0·0001	0·40 (0·23–0·69), p=0·0011
1 year	1·33	6·56	1·00	5·14	0·78 (0·16–3·89), p=0·77	0·79 (0·16–3·87), p=0·77
2 years	1·33	6·57	1·00	4·92	0·75 (0·17–3·24), p=0·70	0·75 (0·18–3·14), p=0·70
3 years	0·67	3·26	0·00	0·00	NC	NC
4 years	0·33	1·63	1·00	4·84	2·98 (0·44–20·05), p=0·26	3·00 (0·47–18·79), p=0·24
5 years	0·17	0·81	0·00	0·00	NC	NC
6 to 14 years	0·67	0·28	2·00	1·07	..	..
21 to 25 years	2·83	2·44	1·50	1·29	..	..

IRRs (with 95% CIs) are shown for the period after vaccination commenced (October, 2018, to September, 2020) versus the pre-vaccination period (October, 2012, to September, 2018) in each age cohort eligible to receive the vaccine. Age cohorts not eligible to receive the vaccine were included but not compared between pre-vaccination and vaccination periods in the adjusted regression model. IRR=incidence rate ratio. NC=not calculable. *Estimated in separate models for each age cohort with population denominators as offset term. †Accounts for changes in the incidence of serogroup B meningococcal disease in age cohorts not eligible to receive the free serogroup B meningococcal disease vaccine.

Table 2: **Incidence of serogroup B meningococcal disease before and 2 years after the commencement of the childhood vaccination programmes**

	Pre-vaccination period		Vaccination period				IRR*	Vaccine-eligibility adjusted IRR†
	Annual mean number of cases	Annual incidence per 100 000 population	Year 1 (February, 2019, to January, 2020)		Year 2 (February, 2020, to January, 2021)			
			Annual number of cases	Annual incidence per 100 000 population	Annual number of cases	Annual incidence per 100 000 population		
<12 weeks	0·13	2·72	0	0	1	22·93	..	..
12 weeks to <1 year	2·63	17·16	1	6·88	1	6·88	0·40 (0·29–0·55), p<0·0001	0·42 (0·26–0·68), p=0·0005
1 to 4 years‡	3·88	4·78	4	4·97	0	0	Year 1: 1·04 (0·77–1·40), p=0·80; Year 2: NC	Year 1: 1·20 (0·73–1·99), p=0·47‡
5 to 14 years	0·63	0·31	4	1·91	0	0	..	..
15 to 18 years	4·00	4·85	2	2·48	0	0	0·26 (0·06–1·15), p=0·08	0·27 (0·06–1·16), p=0·078
19 to 21 years‡	3·88	5·74	4	5·95	0	0	Year 1: 1·04 (0·70–1·54), p=0·86; Year 2: NC	Year 1: 1·20 (0·70–2·06), p=0·51‡
22 to 25 years	1·25	1·34	1	1·06	0	0	..	..

IRRs (with 95% CIs) are shown for the period after vaccination commenced (February, 2019, to January, 2021) versus the pre-vaccination period (February, 2011, to January, 2019) in each age cohort eligible to receive the vaccine. Age cohorts not eligible to receive the vaccine were included but not compared between pre-vaccination and vaccination periods in the adjusted model. IRR=incidence rate ratio. NC=not calculable. *Estimated in separate models for each age cohort with population denominators as offset term. †Accounts for changes in the incidence of serogroup B meningococcal disease in age cohorts not eligible to receive the free serogroup B meningococcal disease vaccine. ‡Catch-up vaccination programmes for these age groups were only offered during the first year after commencement of the programme and therefore IRR was only calculated for the first programme year.

Table 3: **Incidence of serogroup B meningococcal disease before and 2 years after commencement of the adolescent and young adult vaccination programmes**

	Pre-vaccination period		Vaccination period				IRR*	Vaccine-eligibility adjusted IRR†
	Annual mean number of cases	Annual incidence per 100 000 population	Year 1 (February, 2019, to January, 2020)		Year 2 (February, 2020, to January, 2021)			
			Number of cases	Annual incidence per 100 000 population	Number of cases	Annual incidence per 100 000 population		
15 to 17 years	43·38	70·87	59	98·93	40	66·63	1·17 (0·82–1·67), p=0·40	0·76 (0·48–1·22), p=0·26
18 to 20 years‡	104·00	157·99	183	279·38	145	225·68	Year 1: 1·77 (0·89–3·52), p=0·11; Year 2: 1·43 (0·72–2·84), p=0·31	Year 1: 1·24 (0·69–2·24), p=0·47‡
21 to 25 years	209·88	180·84	401	342·75	289	248·56	..	..

IRRs (with 95% CIs) are shown for the period after vaccination commenced (February, 2019, to January, 2021) versus the pre-vaccination period (February, 2011, to January, 2018) in each age cohort eligible to receive the vaccine. Age cohorts not eligible to receive the vaccine were included but not compared between pre-vaccination and vaccination periods in the adjusted regression model. IRR=incidence rate ratio. *Estimated in separate models for each age cohort with population denominators as offset term. †Accounts for changes in the incidence of gonorrhoea in age cohorts not eligible to receive the free serogroup B meningococcal disease vaccine. ‡Adolescent and young adult catch-up programmes were only offered during the first year after commencement of the programme and therefore IRR was only calculated for the first programme year.

Table 4: **Incidence of gonorrhoea before and 2 years after commencement of the adolescent and young adult vaccination programmes**

(two observed cases *vs* 7·55 expected cases; aIRR 0·27 [95% CI 0·06–1·16]; table 3; appendix p 7).

There were two cases of serogroup B meningococcal disease: one reported 65 days after their first dose of 4CMenB and another 103 days after their second dose of 4CMenB. Sequence type cc 41/44 strains ST-146 and ST-154 were identified and associated with Bexsero Antigen Sequence Types 246 and 220, respectively. The screening method, using the date of disease onset and date of birth matched 4CMenB vaccine coverage, showed a two-dose vaccine effectiveness of 94·2% (95% CI 36·6–99·5) against serogroup B meningococcal disease in vaccine-eligible cohorts of children born after Sept 30, 2014. The case-control method, using 20 controls from the South Australian records of the Australian Immunisation Register, showed a two-dose vaccine effectiveness of 94·7% (40·3–99·5) against serogroup B meningococcal disease in vaccine-eligible children.

During the first and second programme years, no cases of serogroup B meningococcal disease were reported in adolescents and young adults who received the vaccine. The vaccine effectiveness was therefore 100%. Variance and confidence limits could not be estimated.

Gonorrhoea and chlamydia notifications increased with age in adolescents and young adults and repeat infection was common across all age groups. The number of gonorrhoea and chlamydia cases declined in the second year of the programme (2020–21) compared with the first year of the programme (2019–20) at different rates across all age groups (appendix p 7).

The fitted negative binomial regression model showed a relative reduction of 24% (aIRR 0·76 [95% CI 0·48–1·22]) in the incidence of gonorrhoea in adolescents aged 15–17 years in the second year of the state 4CMenB vaccination programme compared with the pre-vaccination period (table 4).

Vaccine effectiveness against gonorrhoea was estimated on the basis of people who had gonorrhoea or chlamydia, were born between Feb 1, 1998, and Feb 1, 2005, and had a disease notification date between Feb 1, 2019, and Jan 31, 2021. 512 patients with a total of 575 episodes of gonorrhoea, and 3140 patients with 3847 episodes of chlamydia were included in the analysis.

Using chlamydia infections as controls, vaccine effectiveness was estimated to be 32·6% (95% CI 10·6–49·1) for people who received at least one dose and 32·7% (8·3–50·6) for people who received two doses compared with those who were unvaccinated. Using 20 controls from the Australian Immunisation Register, vaccine effectiveness was estimated to be 61·8% (49·9–70·9) for at least one dose and 62·9% (50·4–72·3) for two doses versus no vaccination. Using the screening method, vaccine effectiveness was estimated to be 70·7% (62·2–77·3) for at least one dose and 73·8% (65·2–80·2) for two doses versus no vaccination.

In the sensitivity analyses, after excluding cases who were co-infected with chlamydia during their first episode of gonorrhoea (n=165), the vaccine effectiveness was 31·6% (1·6–52·5) for people who received two doses compared with people who were unvaccinated. After excluding cases who were co-infected with chlamydia during the first or recurrent episodes of gonorrhoea (n=169), the estimated two-dose vaccine effectiveness was 34·7% (5·5–54·9).

Discussion

Our results provide real-world evidence of the impact and effectiveness of the 4CMenB vaccine against serogroup B meningococcal disease in children and adolescents, and against gonorrhoea in adolescents. The large-scale programme in South Australia is unprecedented within both the Australian and global contexts and provides vital information to guide future global vaccine programmes and policy decisions relating to serogroup B meningococcal disease.

The effectiveness of vaccines targeting uncommon diseases can usually only be assessed after including the vaccination on national or regional immunisation schedules. For 4CMenB, estimates of vaccine effectiveness were published in five countries, obtained during implementation of the publicly funded vaccine programmes in the UK[7,8] and Italy,[5] in a non-funded healthcare setting in Portugal,[9] a state-wide randomised controlled study in Australia,[10] and in regional outbreak control in Canada.[6,21] In the UK, vaccine effectiveness was 52·7% for two doses and 59·1% for three doses 3 years after implementation of the programme.[7] Another study in Canada reported an estimated vaccine effectiveness of 100% during the first 2 years post-campaign, and 79% 4 years after the 4CMenB programme.[6] In two Italian regions, vaccine effectiveness estimates were 93·6% and 91·0%.[5] In Portugal, vaccine effectiveness against serogroup B meningococcal disease was estimated at 79% in fully vaccinated children, and 82% in children who had received at least one dose.[9] Using the same screening method as in the UK study, the estimates of vaccine effectiveness in our study are higher than results reported in the UK, Italy, and Portugal, and close to the estimate (100%) reported in Canada. This higher estimate is likely to be due to the very close match of the antigens in the serogroup B meningococcal disease strain causing the majority of disease in South Australia with the antigens contained in the vaccine.[22] Moreover, because of the small number of serogroup B meningococcal disease cases who received the 4CMenB vaccine, the estimated vaccine effectiveness in our study should be interpreted with caution and is sensitive to fluctuations in cases over time.

The impact of 4CMenB on serogroup B meningococcal disease incidence rates was shown following serogroup B meningococcal disease vaccination in children in the UK[7,8] and Italy,[5] in a population up to 20 years of age in Canada,[6,21] and in adolescents aged 16–19 years in South Australia.[10] In the UK, the incidence rates of serogroup B meningococcal disease decreased by 50% compared with the previous 4 years, with long-term data from the same study showing a 75% reduction during the first 3 years of the immunisation programme.[7,8] The overall impact after versus before the 4CMenB programme showed reductions in disease incidence of 31% in Veneto and 68% in Tuscany.[5] In Canada, the incidence of serogroup B meningococcal disease decreased by 100% in the vaccine-eligible population in the first 2 years of the programme and by 96% after 4 years.[6,21] In a cluster-randomised controlled trial ("B Part of It") conducted in South Australia, vaccination reduced the incidence of serogroup B meningococcal disease by 71% in adolescents aged 16–19 years.[10] This result is very similar to the 73% reduction observed in adolescents aged 15–18 years in the present study. Based on results reported in our study and studies in the UK, Italy, and Canada, the overall reductions tend to be higher in adolescents than infants. Adolescent meningococcal vaccine programmes are more immunogenic and likely to develop broader cross-protection against serogroup B meningococcal disease strains than infant programmes.[23] A statistically non-significant reduction in serogroup B meningococcal disease incidence was observed in young children aged 1–2 years after versus before introduction of the childhood vaccination programme, which might partly be due to a low disease incidence at baseline, but is most likely due to lower vaccine coverage in this age group than in infants aged between 12 weeks and 11 months.

The effect in the second programme year was potentially confounded by public health strategies implemented during the COVID-19 pandemic. Public health interventions reduce the risk of viral respiratory tract infections, including influenza and invasive meningococcal disease. These interventions, aimed against SARS-CoV-2 transmission, might have contributed to reductions in the incidence of serogroup B meningococcal disease incidence and to the impact of the 4CMenB vaccine in 2019–20. However, when the year 1 and year 2 results are considered separately, the vaccine impact for the first year of the childhood programme, before the COVID-19 pandemic, is still significant in infants aged 12 weeks to 11 months.

Since risky sexual behaviours might be a significant confounder associated with gonococcal infections, vaccine effectiveness analyses using controls from the Australian Immunisation Register and the screening method without statistical adjustment for such confounding might not be robust. Only vaccine effectiveness calculated using chlamydia controls is discussed here. The first effective OMV serogroup B meningococcal vaccine (VA-MENGOC-BC) was introduced in Cuba, which implemented a mass vaccination campaign during 1989–90. Epidemiological evidence from Cuba showed that OMV serogroup B meningococcal vaccines could offer cross-protection against gonorrhoea.[12] In a case-control analysis in New Zealand after a campaign using an OMV vaccine (MeNZB), vaccine effectiveness against gonorrhoea was reported as 31%.[11] In the USA, vaccine effectiveness of 4CMenB against gonorrhoea in people aged 16–23 years was assessed in New York City and Philadelphia, and was estimated to be 40% (95% CI 23–53) after two doses.[24] In Canada, a reduction of 59% in the incidence of gonorrhoea was observed in people aged 14–20 years.[25] Similar to the vaccine impact study in Canada, we did not observe a meaningful reduction in the incidence of gonorrhoea, probably due to a small number of gonorrhoea

cases in this age group. However, our study confirmed that effectiveness of the two-dose 4CMenB vaccine against gonorrhoea was around 30% and was associated with a lower risk of gonorrhoea. It has been reported that protein antigens in 4CMenB are presented in *N gonorrhoeae*, and antibodies induced by 4CMenB recognise gonococcal proteins. 4CMenB contains the MeNZB OMV antigen plus three recombinant antigens: *Neisseria* adhesin A (NadA), factor H binding protein (fHbp), and neisserial heparin binding antigen (NHBA). Homologues of 20 core OMV proteins, including PorB, RmpM, OpcA, FbpA, and FrpB, were identified in an *N gonorrhoeae* strain.[26] Gonococcal fHbp was predicted not to be surface-expressed, while NadA was absent in all *N gonorrhoeae* isolates.[15] NHBA is the only 4CMenB recombinant antigen that is exposed on the surface of *N gonorrhoeae*. A high level of homology and cross-reactivity between the meningococcal and gonococcal NHBA proteins suggests that 4CMenB might offer additional cross-protection against gonorrhoea above that estimated for MeNZB.[26]

The factors associated with the prevalence of gonorrhoea and chlamydia co-infections have not been well understood. Cases of co-infection might differ with regard to infection acquisition and transmission and disease course and severity compared with cases of single infection. However, our study showed similar vaccine effectiveness results irrespective of whether co-infected gonorrhoea cases were included or excluded.

A strength of this study lies in the high vaccine coverage in the ongoing programmes and a whole-of-life, national immunisation register that records vaccines given to all people in Australia. However, until recently, it was not mandatory for all vaccination providers to report vaccinations to the Australian Immunisation Register. True coverage is likely to be higher, given possible under-reporting to the register. The enhanced disease surveillance and immunisation register allow for prompt evaluation of vaccine impact and effectiveness. The notifiable condition of invasive meningococcal disease is likely to ensure complete detection of serogroup B meningococcal disease cases.

In patients with repeat episodes of gonorrhoea, only the first recorded diagnosis was included in the analysis. The duration of vaccine protection and vaccine effect on preventing repeat infections were not assessed in this study, because the 4CMenB programme has only been running for 2 years. As 20 controls were selected from the national immunisation register to match each de-identified serogroup B meningococcal disease or gonorrhoea case, there was a small probability that cases might be matched to themselves. However, considering the large number of potentially eligible controls in the national immunisation register, the likelihood of this occurring is very low.

Our study showed a reduction in serogroup B meningococcal disease cases among vaccine-eligible infants, high vaccine effectiveness against serogroup B meningococcal disease in vaccine-eligible cohorts, and cross-protection against gonorrhoea in adolescents and young adults. As 4CMenB does not affect the carriage of *N meningitidis*,[27] direct protection of the highest-risk groups is essential. Our findings of high vaccine effectiveness support the indefinite continuation of the 4CMenB programme in South Australia to protect infants and adolescents against two diseases with one vaccine, and provide essential data to support future vaccine policy nationally and worldwide. Previous modelling studies have shown that even a vaccine efficacy of 20%, which is lower than reported in our study, could result in a substantial reduction in gonococcal infections, transmission, and associated costs.[28,29] Targeted increased access and messaging should be implemented to improve uptake among groups in which 4CMenB vaccine coverage is lower, including Aboriginal and Torres Strait Islander young people. Identifying effective strategies to improve vaccine uptake so that communities are well protected against all meningococcal serogroups, including serogroup B, remains a global challenge.

Contributors

HM led the project. HM, PA, BW, LG, and MM designed the study protocol. LF, AK, SA, NL, MA, and ED were involved in the design of the study. BW and LG performed the analysis. BW wrote the first draft. LF, AK, SA, RB, JM, NL, MA, and ED organised or were involved in data collection. All named authors were involved in the interpretation of data and critical review of the content and have approved the final version for publication. BW and LG accessed and verified all the data. HM had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

HM is an investigator on vaccine trials sponsored by the GSK group of companies, Pfizer, Sanofi, and Merck. The institution of HM, MM, PA, and BW receives funding for investigator-led studies from industry, including Pfizer and Sanofi Pasteur. HM, MM, PA, and BW receive no personal payments from industry. All other authors report no competing interests.

Data sharing

All analyses were performed using de-identified disease notification data provided by the Communicable Disease Control Branch of SA Health, Government of South Australia, and immunisation records provided by the Australian Immunisation Register. The de-identified individual disease notification data with the serogroup B meningococcal disease vaccination history, and a data dictionary defining each field in the set, can be made available to others upon the approval of the Commonwealth Department of Health and the South Australia Department for Health and Wellbeing Human Research Ethics Committee. The study protocol has been published in a peer-reviewed journal. The full study protocol and statistical analysis plan can be made available upon request, by contacting HM or BW.

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