Peer-reviewed version available at *Vaccines* **2019**, *7*, 5; doi:10.3390/vaccines7010005

Effectiveness of a Group B outer Membrane Vesicle Meningococcal Vaccine in Preventing Hospitalization from Gonorrhea in New Zealand: a Retrospective Cohort Study

Janine Paynter, PhD. Research Fellow, Department of General Practice and Primary Health, University of Auckland New Zealand

Felicity Goodyear-Smith, MD. Professor and Head of Department of General Practice and Primary Health Care, University of Auckland New Zealand

Jane Morgan, MD. Clinical Director, Sexual Health Services Waikato District Health Board and Honorary Senior Lecturer, School of Medicine, University of Auckland New Zealand

Peter Saxton, PhD. Senior Research Fellow, Department of Social and Community Health, University of Auckland New Zealand

Steven Black, MD. Professor of Pediatrics, Cincinnati Children's Hospital, Ohio, USA

Helen Petousis-Harris, PhD. Senior Lecturer and Director of Research at Immunisation Advisory Centre, Department of General Practice and Primary Health Care, University of Auckland

Corresponding author

Dr Janine Paynter, Research Fellow

Department of General Practice and Primary Health Care,

Faculty of Medical & Health Science, University of Auckland, PB 92019 Auckland 1142

Telephone +64 9 923 3806; email j.paynter@auckland.ac.nz

KEY WORDS

Gonorrhea; Outer membrane vesicle vaccine; Group B meningococcus; Cohort study; New Zealand

Word count of manuscript

Peer-reviewed version available at Vaccines 2019, 7, 5; doi:10.3390/vaccines7010005

ABSTRACT

Gonorrhea is a major global public health problem with emergence of multiple drug-resistant strains with no effective vaccine. This retrospective cohort study aimed to estimate the effectiveness of the New Zealand meningococcal B vaccine against gonorrhea associated hospitalization. The cohort consisted of individuals born 1984-1999 residing in New Zealand, therefore eligible for meningococcal B vaccination during 2004-2008. Administrative datasets of demographics, customs, hospitalization, education, income tax and immunization, were linked using the national Integrated Data Infrastructure. The primary outcome was hospitalization with a primary diagnosis of gonorrhea. Cox's proportional hazards models were applied with a Firth correction for rare outcomes to generate estimates of hazard ratios. Vaccine effectiveness estimates were calculated as 1-Hazard Ratio expressed as percent. There were 1,143,897 eligible cohort members, with 135 missing information on gender, 16,245 missing ethnicity and/or 197,502 missing deprivation hence 935,496 were included in the analysis. After adjustment for gender, ethnicity and deprivation, vaccine effectiveness (MeNZB™) against hospitalization caused by gonorrhea was estimated to be 24% (95% CI 1-42%). In conclusion, vaccination with MeNZB™ significantly reduced the rate of hospitalization from gonorrhea. This supports prior research indicating possible cross protection of this vaccine against gonorrhea acquisition and disease in the outpatient setting.

INTRODUCTION

Gonorrhea is a major international public health problem[1,2], now exacerbated by the increasing emergence of multiple drug-resistant strains [3-5]. To date, development of an effective vaccine has been unsuccessful [6]. Contracting the infection does not provide immunity and hence repeated infections can commonly occur [7]. Unfortunately there is no immunological correlate of protection to guide vaccine development.

Since gonorrhea is a reportable disease in most developed countries, the incidence trends over time are relatively easy to track. Using such ecological data from national disease surveillance reports, a decline in gonorrhea in the period immediately following use of group B meningococcal outer membrane vesicles (OMV) vaccines in Cuba,[8] New Zealand (NZ),[10] and to a limited extent, Norway [9,10], suggested that meningococcal B OMV vaccines may reduce the risk of gonorrhea. The 80 to 90% genetic homology between *Neisseria meningitidis* and *N. gonorrhoeae* offers a biologically plausible mechanism by which cross protection might occur [11].

In NZ, 81% of the population aged 0 to 20 years received doses of the strain-specific OMV meningococcal B (MeNZB™) vaccine from 2004 through schools and primary care, in response to a prolonged epidemic of group B meningococcal disease [12]. The mass immunization program ran for two years from 2004 to 2006, and the vaccine was available until 2008. Approximately one million infants, children and young people received all three doses of the vaccine. In NZ everyone is assigned a National Health Index number (NHI). This unique person–specific alphanumeric identifier is used across all health systems and makes data linkage relatively simple and robust.

This infrastructure enabled us to conduct a case-control study using immunization and sexual health clinic data to evaluate the vaccine effectiveness (VE) of the 3+0 (three primary doses, no booster) schedule of MeNZB™, used in NZ in 2004-2008, against confirmed gonorrhea cases between 2004 and 2016 in young adults aged 15–30 years. From the sample of this study (14,730 cases and controls for analyses consisting of 1,241 incidences of gonorrhea, 12,487 incidences of chlamydia and 1,002 incidences of co-infection) we were able to

determine that those vaccinated were less likely to be cases (41% vs 49%, adjusted OR 0.69 (95%CI 0.61-0.79), and after adjusting for ethnicity, deprivation (socio-economic status), geographic area and gender, we found a VE of 31% (95% CI 21-39) [13].

In addition to cases presenting at sexual health clinics and primary care, gonorrhea may also be associated with significant morbidity including pelvic inflammatory disease, ectopic pregnancy, infertility and chronic pain. An Australian retrospective cohort study found 5% (45 out of 1015) women diagnosed with gonorrhea were subsequently hospitalized with pelvic inflammatory disease, whereas only 1.3% (483/38,193) with chlamydia were hospitalized [14]. Similarly, gonorrhea may result in hospitalization for orchitis or epididymitis in men.

We wished to explore the effectiveness of the MeNZB™ vaccine in reducing hospitalizations from gonorrhea in the same study population as our case-control study. Our aim was to estimate the VE of the 3+0 immunization series against gonorrhea-associated hospitalization using a retrospective cohort study.

MATERIALS AND METHODS

This is a retrospective cohort study design.

Study population

The study population is NZ residents born 1984 to 1999 inclusive who were residing in NZ from 2004 (the start of the MeNZB program), through until 2015. Cohort eligibility (i.e. residence in NZ) was determined using the NHI demographic dataset;, Customs New Zealand journey information (all arrivals and departures via New Zealand ports from 1997; secondary and tertiary education data; the National Immunisation Register (NIR), and a restricted subset of income tax data records. Record linkage was through use of the Integrated Data Infrastructure (IDI) provided by Statistics NZ [15]. Deaths prior to 2004, and those who were absent from NZ from or before Jan 2004, as indicated by travel data or lack of presence in the education, tax, health and address notifications datasets were excluded from the study. Logic checks were done to remove mismatched linked data (for example, individuals with travel

dates occurring earlier than birth date). This population is drawn from the same population from which the earlier case-control study participants were selected [13].

Vaccination status and other descriptive variables

Cohort members were considered fully vaccinated if they had received three doses of the MeNZB™ vaccine. Members who had one or two doses were considered partially vaccinated. Information on vaccine doses and dates was obtained from the National Immunisation Register.

Ethnicity (priority coded Māori, Pacific Island and NZ European/Asian/other) and gender are provided in the NHI dataset. Where available, decile deprivation is estimated using each cohort members' most recent residential mesh block and the New Zealand deprivation index.[16] A value of 1 indicates a meshblock is in the 10% least deprived areas in NZ; a value of 10 is the 10% most deprived. The deciles are collapsed in this study to three groups low, medium and high deprivation.

Risk of contracting gonorrhea is associated with sexual activity therefore the likely age of sexual debut impacts on the risk of gonorrhea and other sexually transmitted diseases. There was a wide age range (4-20 years) among our cohort at the start of the vaccination program in 2004. The reported average age for sexual debut in NZ is 15-16 years with very few young people reporting sexual activity before 13 years [17]; therefore, the age at which each cohort member turns 13 was chosen as the start date for follow-up in our study.

Outcome variables/events

The primary outcome considered in this analysis is hospitalization with gonorrhea, where gonorrhea is considered the reason for hospitalization of cohort members. Table 1 shows the specific ICD-10-AM codes used. Selection of the diagnosis codes was made by members of the team with clinical experience in the area of sexually transmitted disease and broader consultation with clinicians working in this area. Group 1 is the most specific, because these codes identify gonococcal bacteria as the cause. Prior to accessing the data we were unsure how many outcomes there would be that were specifically attributable to gonorrhea, therefore

we decided a priori on a set of conditions that may be caused by gonorrhea. Group 2 were genitourinary infections which, based on our clinical experience and knowledge of the literature, may be frequently caused by gonorrhea as well as by other organisms (such as chlamydia). Group 3 are conditions with a range of causative agents, for which gonorrhea-attributable cases will be a small minority.

Table 1: ICD10 codes used to identify primary (main reason for) hospitalizations of interest

ICD10 Code	Text description	Gonorrhea only	Outcome 2	Outcome 3
A54.0	Gonococcal infection including cervicitis, cystitis, urethritis, vulvovaginitis	Yes	Yes	Yes
A54.2	Gonococcal pelviperitonitis including epididymitis, female pelvic inflammatory disease, orchitis, prostatitis	Yes	Yes	Yes
A54.3	Gonococcal conjunctivitis	Yes	Yes	Yes
A54.4	Gonococcal infection of musculoskeletal system	Yes	Yes	Yes
A54.8	Other gonococcal infections including meningitis, septicaemia	Yes	Yes	Yes
A54.9	Gonococcal infection, unspecified	Yes	Yes	Yes
O98.2	Gonorrhea complicating pregnancy	Yes	Yes	Yes
N74.3	Female gonococcal pelvic inflammatory disease	Yes	Yes	Yes
N41.0	Acute prostatitis	No	Yes	Yes
N41.2	Abscess of prostate	No	Yes	Yes
N41.9	Inflammatory disease of prostate, unspecified	No	Yes	Yes
N45.0	Orchitis, epididymitis and epididymo-orchitis with abscess	No	Yes	Yes
N45.9	Orchitis, epididymitis and epididymo-orchitis without abscess	No	Yes	Yes
N70.0	Acute salpingitis and oophoritis	No	Yes	Yes
N70.1	Chronic salpingitis and oophoritis	No	Yes	Yes
N70.9	Salpingitis and oophoritis, unspecified	No	Yes	Yes
N71.0	Acute inflammatory disease of uterus	No	Yes	Yes

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 June 2018 doi:10.20944/preprints201806.0495.v1

Peer-reviewed version available at Vaccines 2019, 7, 5; doi:10.3390/vaccines7010005

N71.1	Chronic inflammatory disease of uterus	No	Yes	Yes
N71.9	Inflammatory disease of uterus, unspecified	No	Yes	Yes
N72.0	Inflammatory disease of cervix uteri	No	Yes	Yes
N73.0	Acute parametritis and pelvic cellulitis	No	Yes	Yes
N73.1	Chronic parametritis and pelvic cellulitis	No	Yes	Yes
N73.2	Parametritis and pelvic cellulitis, unspecified	No	Yes	Yes
N73.8	Other specified female pelvic inflammatory disease	No	Yes	Yes
N73.9	Female pelvic inflammatory disease, unspecified	No	Yes	Yes
J02.9	Acute pharyngitis	No	No	Yes
K62.8	Other specified diseases of anus and rectum, proctitis NOS	No	No	Yes
N41.1	Chronic prostatitis	No	No	Yes
N48.2	Other inflammatory diseases of penis	No	No	Yes
N73.3	Female acute pelvic peritonitis	No	No	Yes
N73.5	Female pelvic peritonitis, unspecified	No	No	Yes
N73.6	Female pelvic peritoneal adhesions	No	No	Yes
N75.0	Cyst of Bartholin's gland	No	No	Yes
N75.1	Abscess of Bartholin's gland	No	No	Yes
N75.8	Other diseases of Bartholin's gland	No	No	Yes
N75.9	Disease of Bartholin's gland, unspecified	No	No	Yes
N76.0	Acute vaginitis	No	No	Yes
N76.1	Subacute and chronic vaginitis	No	No	Yes
N76.2	Acute vulvitis	No	No	Yes
N76.3	Subacute and chronic vulvitis	No	No	Yes
N76.4	Abscess of vulva	No	No	Yes
N76.5	Ulceration of vagina	No	No	Yes
N76.6	Ulceration of vulva	No	No	Yes

Table 3: Cox's proportional hazards with Firth correction for rare events estimates and 95% confidence intervals (CI) for the primary outcome (hospitalization with gonorrhea was specified)

	Hospitalization with Gonorrhea

Peer-reviewed version available at Vaccines 2019, 7, 5; doi:10.3390/vaccines7010005

	Yes	%	Total	HR	Adjusted HR
Gender					
Missing	S	S	135	NA	NA
Female	213	(0.038)	558,162		Ref
Male	48	(0.008)	585,603		0.22 (0.16-0.30)
Ethnicity					
Missing	S	S	16,245		
European & other	45	(0.006)	718,704		Ref
Māori	198	(0.067)	293,529		8.44 (5.87-12.13)
Pacific Peoples	18	(0.016)	115,422		2.04 (1.12-3.73)
Deprivation					
Missing	36	(0.018)	197,511		NA
High	144	(0.041)	351,321		2.30 (1.42-3.75)
Medium	63	(0.018)	358,080		1.55 (0.93-2.57)
Low	18	(0.008)	236,982		Ref
Vaccination status					
Unvaccinated	129	(0.028)	466,710		Ref
Partial	S	S	S	0.42 (0.08-2.12)	0.31 (0.06-1.57)
Vaccinated	132	(0.019)	677,190	0.89 (0.69-1.16)	0.76 (0.58-0.99)
Total	**261**	**(0.023)**	**1,143,897**		

Table 4: Cox's proportional hazards with Firth correction for rare events estimates and 95% confidence intervals (CI) for group 2 outcomes

	Hospitalization with Gonorrhea or a Group 2 Diagnosis				
	Yes	**%**	**Total**	**HR**	**Adjusted HR**
Gender					
Missing	S	S	135	NA	NA
Female	3,945	0.71	558,162		Ref
Male	1,443	0.25	585,600		0.34 (0.32-0.36)
Ethnicity					
Missing	S	S	16,245	NA	NA
European & Other	2,202	0.31	718,704		Ref
Māori	2,652	0.90	293,529		2.45 (2.29-2.61)
Pacific Peoples	531	0.46	115,422		1.41 (1.27-1.57)
Deprivation					
Missing	729	0.37	197,511	NA	NA
High	2,319	0.66	351,321		1.40 (1.29-1.53)
Medium	1,578	0.44	358,083		1.15 (1.05-1.25)
Low	762	0.32	236,985		Ref

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 29 June 2018 doi:10.20944/preprints201806.0495.v1

Peer-reviewed version available at Vaccines 2019, 7, 5; doi:10.3390/vaccines7010005

Vaccination status					
Unvaccinated	2,169	0.46	466,710		Ref
Partial	96	0.83	11,547	1.65 (1.32-2.01)	1.45 (1.16-1.82)
Vaccinated	3,123	0.47	665,640	1.36 (1.29-1.45)	1.28 (1.21-1.36)
Total	**5,385**	**0.47**	**1,143,897**		

Table 5: Cox's proportional hazards with Firth correction for rare events estimates and 95% confidence intervals (CI) for group 3 outcomes

	Hospitalization with Gonorrhea, Group 2 or Group 3 diagnosis				
	Yes	**%**	**Total**	**HR**	**Adjusted HR**
Gender					
Missing	S	S	135		NA
Female	6,579	1.18	558,162		Ref
Male	2,031	0.35	585,600		0.28 (0.27-1.41)
Ethnicity					
Missing	S	S	16,245		NA
European & Other	3,936	0.55	718,704		Ref
Māori	3,828	1.30	293,529		2.00 (1.90-2.10)
Pacific Peoples	846	0.73	115,422		1.28 (1.18-1.39)
Deprivation					
Missing	1,173	0.59	197,511		NA
High	3,525	1.00	351,321		1.37 (1.29-1.47)
Medium	2,640	0.74	358,080		1.18 (1.10-1.26)
Low	1,272	0.54	236,985		Ref
Vaccination status					
Unvaccinated	3,438	0.74	466,710		Ref
Partial	150	1.30	11,547	1.64 (1.37-1.96)	1.49 (1.24-1.78)
Vaccinated	5,025	0.75	665,640	1.41 (1.35-1.48)	1.34 (1.28-1.41)
Total	**8,610**	**0.75**	**1,143,897**		

Statistical analysis

Descriptive statistics (frequencies and percentages) are presented for each of the main variables of interest. In order to meet the privacy protection requirements of Statistics New Zealand each count (both population and numbers of cases) has been randomly rounded to a base of 3. Percentages are based on rounded counts. Counts with original values <6 are suppressed and identified in this report as S.

Cox's proportional hazards models (proc PHREG as per SAS Enterprise Guide v7.1) were applied with a Firth correction [18] for rare outcomes and predictive covariates in order to generate estimates of hazard ratios. Vaccination status is modelled as a time–dependent variable. Individuals who did not receive any doses of MeNZB™ were unvaccinated for all of follow-up. Individuals who had received three doses prior to their 13th birthday were vaccinated for all of follow-up. Those who had received one or two doses before follow-up were partially vaccinated. If unvaccinated before follow-up then status changed on receipt of the first dose from unvaccinated to partial. Receipt of a third dose during follow-up changed status from partial to vaccinated. Univariate and multivariable model estimates are presented. Cohort members were right censored if they died or left NZ for longer than 6 weeks after start of follow-up (13th birthday) before hospitalization or the end of the study period, 31st Dec 2015. Six weeks was chosen in order to minimize the bias which may occur from a cohort member being hospitalized overseas, and therefore not recorded in our data, but allow for the relatively common practice for young New Zealanders of an overseas vacation. Unrounded data was used as model input. The VE estimates are calculated as 1-Hazard Ratio and expressed as a percent. Unit of follow up time was set as groups of 30 days (approximation of months) from the start date (13th birthday).

Ethical approval was obtained from NZ's Health and Disability Ethics Committee (Reference 15/CEN/189).

RESULTS

Our primary outcome was defined as a hospitalization specifically due to gonorrhea infection. There were 1,143,897 eligible cohort members, NZ residents born 1984 to 1999 inclusive residing in NZ from age of 13 years and including years 2004 through until 2015. There were 135 individuals missing information on sex, 16,245 missing ethnicity and/or 197,502 missing deprivation. Therefore 935,496 individuals, with data on sex, ethnicity and deprivation were included in the analysis. Just under half of the cohort (48.8%) were female. Europeans were the largest ethnic group, and were combined with the two other smallest groups, other and Asian, forming 62.3% of the cohort. Māori were a quarter of the cohort (25.7%) and Pacific Island ethnicities made up the remaining 10% of the cohort. Twenty-one percent of the cohort

lived in an area of low deprivation, about thirty percent of medium deprivation, and another 30% l of high deprivation. The largest proportion of missing data was on deprivation (17%).

Table 2 shows a demographic breakdown of the cohort and vaccination status. There was only minor difference in vaccinated coverage by gender. Māori compared to Europeans, other ethnicities and Pacific Peoples were more likely to be vaccinated. Vaccination coverage was similar across deprivation levels. The middle and younger aged members of the cohort were more likely to be vaccinated with only 32% of those born 1984-1988 vaccinated, compared to 74% of those born 1989-1993 vaccinated, and 77% of those born in 1994-1999.

Table 2: Associations between co-variates and vaccination status

Co-variate	Partially vaccinated	(%)	Unvaccinated	(%)	Vaccinated	(%)	Total[2]
Gender							
Female	5,343	(1.0)	225,243	(40.4)	327,576	(58.7)	558,162
Male	6,204	(1.1)	241,338	(41.2)	338,061	(57.7)	585,600
Ethnicity							
European & Other	5,082	(0.7)	308,016	(42.9)	405,606	(56.4)	718,704
Māori	4,806	(1.6)	91,767	(31.3)	196,959	(67.1)	293,529
Pacific Peoples	1,584		51,768		62,067	(53.8)	115,422
Deprivation							
Low	1,932	(0.8)	86,910	(36.7)	148,143	(62.5)	236,985
Medium	3,075		138,690	(38.7)	216,315	(60.4)	358,080
High	4,710	(1.3)	137,940	(39.3)	208,671	(59.4)	351,321
Hospitalization							
None	11,397	(1.0)	463,272	(40.8)	660,615	(58.2)	1,135,287
Gonorrhea only	S[1]		132	(50.6)	S		261
Group 2 only	90	(1.8)	2,037	(39.8)	2,997	(58.5)	5,124

Group 3 only	S	1,266	(39.3)	S		3,225

[1] S indicates that this value has been suppressed as per Statistics NZ to protect privacy and confidentiality.

[2] Counts have been randomly rounded to base 3 as per Statistics NZ to protect privacy and confidentiality and may not reconcile precisely.

A relatively small proportion (1%) of the cohort was partially vaccinated (about 11,547) compared to those either unvaccinated (41%) or vaccinated (58%). This group of partially vaccinated individuals also had a higher proportion of Māori and those with the highest deprivation compared to unvaccinated and vaccinated groups.

There were 261 cases of first hospitalization attributable to gonorrhea specifically, making this a rare outcome. Hospitalizations (5,124) with a group 2 condition were the most common. Finally there were 3,225 hospitalizations in the group 3 categories. For analysis outcomes these hospitalizations combined as follows: outcome one was a hospitalization specifically attributable to gonorrhea; outcome two was a hospitalization specifically attributable gonorrhea or a group 2 condition so the combined number of outcomes was 5,385; outcome three was a combination of hospitalizations specifically attributable to gonorrhea, group 2 and group 3 conditions, a total of 8610. The outcomes 1-3 decrease in specificity.

Hospitalized cases were more likely to be female for outcomes one, two and three (Tables 3-5). Those in the highest deprivation were also more likely to be hospitalized for all three outcomes. However, Māori were notably much more likely, Hazard Ratio = 8 (6-12 95% CI) to be hospitalized with a gonorrhea specified outcome compared to NZ Europeans and other (Table 3). There was less disparity between Māori and NZ Europeans and other when considering group 2 and group 3 outcomes (Tables 4-5).

Vaccinated individuals were significantly less likely to be hospitalized due to gonorrhea after adjusting for gender, ethnicity and deprivation (HR 0.76, 95% CI 0.58-0.99). A small to medium effect size. This gives a vaccine effectiveness estimate of 24% (95% CI 1-42%).

Vaccination was significantly associated with an increased risk of hospitalization (HR 1.28, 95% CI 1.21-1.36 for outcome 2, HR 1.34, 95% CI 1.28-1.41 for outcome 3) when outcomes

included a range of conditions likely to be caused by other sexually transmitted organisms, for example chlamydia, which is more common than gonorrhea. This was also small to medium effect.

DISCUSSION

Vaccines may protect against infection, prevent disease and/or mitigate disease severity [19,20]. We found evidence that MeNZB™ may be moderately effective at preventing hospitalization specifically attributable to gonorrhea with an estimated vaccine effectiveness of 24%. This is slightly lower the vaccine effectiveness estimate for prevention of cases of gonorrhea presenting at sexual health clinics (31%) [13].

When considering hospitalization attributable to sexually transmitted disease more broadly (outcomes two and three), the study found an increased risk (small effect) of hospitalization amongst vaccinated individuals. These outcomes were much less specific and there is likely to be a number of factors, including bias due to misclassification i.e. sexually transmitted diseases not due to gonorrhea, which contribute to this finding. However the most likely explanation is that our predominantly unvaccinated older cohort were in the study for a longer period. End of follow-up was the date up to which we had data on hospitalizations in order to maximize the number of cases (hence power) of a rare outcome. Risk of acquiring a sexually transmitted infection is lower after 24 years. The older members of the cohort would have reached and been beyond this and they were more likely to be unvaccinated and at lower risk. In addition for the younger cohort members there is more time elapsed between vaccination and risk of a sexually transmitted infection so there may be waning of the vaccine effect.

What is important about the difference in effect of vaccination for the outcome 1 (gonorrhea specific) versus more non-specific outcomes 2 and 3, is that outcomes 2 and 3 provide a reasonable broader measure of risk of hospitalization due to sexually transmitted infection in the vaccinated versus unvaccinated population. This strengthens the case for an effect of the vaccine per se and not an artefact of confounding due to a difference in risky sexual

behaviors between vaccinated versus unvaccinated found in both this study and our earlier case-control study drawn from the same population [13].

Strengths

We were able to link a number of datasets using the unique NHI number to establish a robust cohort which met our eligibility criteria. The use of large administrative datasets enables us to capture a large proportion (almost all) of the New Zealand population and therefore investigate the impact of the vaccine on a rarer, more severe outcome.

Limitations

Hospitalizations due to gonorrhea represent only the very severe end of the disease spectrum and are also very rare. We have adjusted for this in the analysis but this may still lead to an overestimate of vaccine effectiveness.

We have assumed age as an indicator of commencement of sexual activity and therefore risk of getting a sexually transmitted infection. The start of follow up was set at 13 years however there are likely to have been many who were not sexually active and therefore not at risk until much older e.g. 18 years. This is only of concern if there is likely to be a strong association between age of onset of sexual activity and likelihood of vaccination. Given that the vaccination program was school based and achieved good coverage, including for groups perceived at higher risk of poor outcomes, this is unlikely.

The rarity of the outcome also makes it difficult to draw meaningful inferences about vaccine effectiveness for specific subgroups such as Māori.

In our case control study we found a 31% VE against gonococcal infection [13]. This current cohort study suggests that MeNZB™ may afford 24% VE against hospitalization for gonorrhea. Gonorrheal infection is a spectrum ranging from very mild or asymptomatic to a serious systemic and life-threatening disease. It is likely that in some cases the vaccine does

not completely prevent infection, but provides sufficient cross-protection so that only a mild case of the disease is experienced.

This was an observational study using data which was not collected with the purpose of investigating the impact of the MeNZB™ on gonorrhea. Whilst we have incorporated data on common confounders, there may still be unknown confounding influences on the outcome.

Protection against gonococcal infection would impart considerable public health benefits, particularly with the global increase in antimicrobial resistant strains. Our findings lend further weight to the premise that it should be possible to develop an OMV gonorrhea-specific vaccine.

ACKNOWLEDGEMENTS

We acknowledge Professor Diana Lennon and all involved in the development and implementation of the MeNZB™ vaccination program.

FUNDING

This research was funded by Novartis Vaccines & Diagnostics AG (a member of the GlaxoSmithKline group) and sponsored by Auckland UniServices Ltd. The sponsors had no role in the design of the study, in the collection, analyses, or interpretation of data; in the writing of this manuscript, and in the decision to publish the results.

AUTHOR CONTRIBUTIONS

Conceptualization, Janine Paynter, Felicity Goodyear-Smith and Helen Petousis-Harris; Formal analysis, Janine Paynter; Funding acquisition, Felicity Goodyear-Smith and Helen Petousis-Harris; Investigation, Janine Paynter, Peter Saxton, Steve Black and Helen Petousis-Harris; Methodology, Janine Paynter, Felicity Goodyear-Smith, Jane Morgan, Peter Saxton, Steve Black and Helen Petousis-Harris; Project administration, Helen Petousis-Harris; Writing – original draft, Felicity Goodyear-Smith; Writing – review & editing, Janine Paynter, Felicity Goodyear-Smith, Jane Morgan, Peter Saxton, Steve Black and Helen Petousis-Harris.

CONFLICTS OF INTEREST

HPH has been a consultant for GSK, Merck and Pfizer but has not received an honorarium. SB has been a consultant for Novartis Vaccines and is currently a consultant for GSK, Protein Sciences, Merck and WHO.

DISCLAIMER

The results in this paper are not official statistics, they have been created for research purposes from the Integrated Data Infrastructure (IDI), managed by Statistics New Zealand. The opinions, findings, recommendations, and conclusions expressed in this paper are those of the author, not Statistics NZ. Access to the anonymized data used in this study was

provided by Statistics NZ in accordance with security and confidentiality provisions of the Statistics Act 1975. Only people authorized by the Statistics Act 1975 are allowed to see data about a particular person, household, business, or organization, and the results in this paper have been made confidential to protect these groups from identification. Careful consideration has been given to the privacy, security, and confidentiality issues associated with using administrative and survey data in the IDI. Further detail can be found in the Privacy impact assessment for the Integrated Data Infrastructure available from www.stats.govt.nz.

REFERENCES

1. Newman, L.; Rowley, J.; Vander Hoorn, S.; Wijesooriya, N.S.; Unemo, M.; Low, N.; Stevens, G.; Gottlieb, S.; Kiarie, J.; Temmerman, M. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PloS one* **2015**, *10*, e0143304.
2. Tramont, E.C. Gonococcal vaccines. *Clin Microbiol Rev* **1989**, *2 Suppl*, S74-77.
3. Lewis, D.A. Global resistance of neisseria gonorrhoeae: When theory becomes reality. *Curr Opin Infect Dis* **2014**, *27*, 62-67.
4. Bolan, G.A.; Sparling, P.F.; Wasserheit, J.N. The emerging threat of untreatable gonococcal infection. *N Engl J Med* **2012**, *366*, 485-487.
5. Kirkcaldy, R.D.; Harvey, A.; Papp, J.R.; Del Rio, C.; Soge, O.O.; Holmes, K.K.; Hook, E.W., 3rd; Kubin, G.; Riedel, S.; Zenilman, J., *et al.* Neisseria gonorrhoeae antimicrobial susceptibility surveillance - the gonococcal isolate surveillance project, 27 sites, united states, 2014. *MMWR Surveill Summ* **2016**, *65*, 1-19.
6. Edwards, J.L.; Jennings, M.P.; Apicella, M.A.; Seib, K.L. Is gonococcal disease preventable? The importance of understanding immunity and pathogenesis in vaccine development. *Critical Reviews in Microbiology* **2016**, 1-14.
7. Mehta, S.D.; Erbelding, E.J.; Zenilman, J.M.; Rompalo, A.M. Gonorrhoea reinfection in heterosexual std clinic attendees: Longitudinal analysis of risks for first reinfection. *Sex Transm Infect* **2003**, *79*, 124-128.
8. Pérez, O.; J, d.C.; M, C.; E, G.; N, N.; O, C.; R, L.; R, A.; C, Z.; J, B., *et al.* Mucosal approaches in neisseria vaccinology. *VacciMonitor* **2009**, *18*, 53-55.
9. STI Surveillance Team. *Sexually transmitted infections in new zealand: Annual surveillance report 2009*; Institute of Environmental Science and Research Limited: Wellington, New Zealand, 2010.
10. Whelan, J.; Kløvstad, H.; Haugen, I.; Holle, M.; Storsaeter, J. Ecologic study of meningococcal b vaccine and neisseria gonorrhoeae infection, norway. *Emerging infectious diseases* **2016**, *22*, 1137.
11. Tinsley, C.R.; Nassif, X. Analysis of the genetic differences between neisseria meningitidis and neisseria gonorrhoeae: Two closely related bacteria expressing two different pathogenicities. *Proceedings of the National Academy of Sciences* **1996**, *93*, 11109-11114.

12. Arnold, R.; Galloway, Y.; McNicholas, A.; O'Hallahan, J. Effectiveness of a vaccination programme for an epidemic of meningococcal b in new zealand. *Vaccine* **2011**, *29*, 7100-7106.
13. Petousis-Harris, H.; Paynter, J.; Morgan, J.; Saxton, P.; McArdle, B.; Goodyear-Smith, F.; Black, S. Effectiveness of a group b omv meningococcal vaccine against gonorrhoea in new zealand - a case control study. *Lancet* **2017**, *390*, 1603-1610.
14. Reekie, J.; Donovan, B.; Guy, R.; Hocking, J.S.; Jorm, L.; Kaldor, J.M.; Mak, D.B.; Preen, D.; Pearson, S.; Roberts, C.L., *et al.* Hospitalisations for pelvic inflammatory disease temporally related to a diagnosis of chlamydia or gonorrhoea: A retrospective cohort study. *PLoS ONE* **2014**, *9*, e94361.
15. Statistics New Zealand. *Linking methodology used by statistics new zealand in the integrated data infrastructure project*; Wellington, Jun, 2014; p 31.
16. Salmond, C.E.; Crampton, P. Development of new zealand's deprivation index (nzdep) and its uptake as a national policy tool. *Can J Public Health* **2012**, *103*, S7-11.
17. Clark, T.C.; Moselen, E.; Dixon, R.; The Adolescent Health Research Group; Lewycka, S. *Sexual and reproductive health and sexual violence among new zealand secondary students: Findings form the youth'12 national youth health and wellbeing survey*; The University of Auckland: Auckland, New Zealand, 2015.
18. Heinze, G.; Schemper, M. A solution to the problem of monotone likelihood in cox regression. *Biometrics* **2001**, *57*, 114-119.
19. Schmitt, H.J.; von Konig, C.H.; Neiss, A.; Bogaerts, H.; Bock, H.L.; Schulte-Wissermann, H.; Gahr, M.; Schult, R.; Folkens, J.U.; Rauh, W., *et al.* Efficacy of acellular pertussis vaccine in early childhood after household exposure. *Jama* **1996**, *275*, 37-41.
20. Preziosi, M.P.; Halloran, M.E. Effects of pertussis vaccination on disease: Vaccine efficacy in reducing clinical severity. *Clin Infect Dis* **2003**, *37*, 772-779.