Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

Summary

Background **Gonorrhoea is a major global public health problem that is exacerbated by drug resistance. Effective vaccine development has been unsuccessful, but surveillance data suggest that outer membrane vesicle meningococcal group B vaccines affect the incidence of gonorrhoea. We assessed vaccine effectiveness of the outer membrane vesicle meningococcal B vaccine (MeNZB) against gonorrhoea in young adults aged 15–30 years in New Zealand.**

Methods **We did a retrospective case-control study of patients at sexual health clinics aged 15–30 years who were born between Jan 1, 1984, and Dec 31, 1998, eligible to receive MeNZB, and diagnosed with gonorrhoea or chlamydia, or both. Demographic data, sexual health clinic data, and National Immunisation Register data were linked via patients' unique personal identifier. For primary analysis, cases were confirmed by laboratory isolation or detection of *Neisseria gonorrhoeae* only from a clinical specimen, and controls were individuals with a positive chlamydia test only. We estimated odds ratios (ORs) comparing disease outcomes in vaccinated versus unvaccinated participants via multivariable logistic regression. Vaccine effectiveness was calculated as 100×(1–OR).**

Findings **11 of 24 clinics nationally provided records. There were 14 730 cases and controls for analyses: 1241 incidences of gonorrhoea, 12 487 incidences of chlamydia, and 1002 incidences of co-infection. Vaccinated individuals were significantly less likely to be cases than controls (511 [41%] *vs* 6424 [51%]; adjusted OR 0·69 [95% CI 0·61–0·79]; p<0·0001). Estimate vaccine effectiveness of MeNZB against gonorrhoea after adjustment for ethnicity, deprivation, geographical area, and sex was 31% (95% CI 21–39).**

Interpretation **Exposure to MeNZB was associated with reduced rates of gonorrhoea diagnosis, the first time a vaccine has shown any protection against gonorrhoea. These results provide a proof of principle that can inform prospective vaccine development not only for gonorrhoea but also for meningococcal vaccines.**

Funding **GSK Vaccines.**

Published **Online** July 10, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31449-6

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(17)31605-7

Department of General Practice and Primary Health Care (H Petousis-Harris PhD, J Paynter PhD, Prof F Goodyear-Smith MD), **School of Medicine** (J Morgan MD), **Department of Social and Community Health** (P Saxton PhD), **and Conectus, Auckland Uniservices** (B McArdle MCE), **University of Auckland, Auckland, New Zealand; Sexual Health Services, Waikato District Health Board, Hamilton, New Zealand** (J Morgan); **and Center for Global Health, Cincinnati Children's Hospital, Cincinnati, OH, USA** (Prof S Black MD)

Correspondence to: Dr Helen Petousis-Harris, Department of General Practice and Primary Health Care, Faculty of Medical and Health Sciences, University of Auckland, PB 92019 Auckland 1142, New Zealand **h.petousis-harris@auckland.ac.nz**

Introduction

Gonorrhoea is associated with significant morbidity, including pelvic inflammatory disease, infertility, and chronic pain, and is a major global public health concern, with an estimated 78 million incident new cases each year.[1,2] Antimicrobial resistance has grown steadily since the 1940s, and extensively drug-resistant strains of gonorrhoea have emerged.[3–5]

Efforts to develop an effective vaccine against gonorrhoea have been unsuccessful despite more than a century of research.[6] Natural infection does not induce protective immunity, with repeated infection common.[7] Challenges for vaccine development include the absence of a correlate of protection, the absence of a suitable animal model, subversion and evasion of the immune response by the gonococcus to favour survival, and high antigenic variability. The four candidates that reached clinical trials were a therapeutic whole-cell vaccine,[8] a partly autolysed vaccine,[9,10] a pilin vaccine,[11] and a PorA vaccine, none of which were effective.[6,12,13] However, ecological data suggest a decline in gonorrhoea in the period immediately after use of group B meningococcal outer membrane vesicle (OMV) vaccines in Cuba,[14] New Zealand,[10] and, to some extent, Norway,[15,16] suggesting that OMV vaccines could affect the incidence of gonorrhoea.

OMV vaccines are generally only thought to be useful against epidemics dominated by strains belonging to the same meningococcal porin group or serosubtype.[17] Ecological data suggest a reduction in cases of gonorrhoea among the population eligible for OMV meningococcal B vaccination. Despite the differences in disease manifestation, there is 80–90% genetic homology in primary sequences between *Neisseria gonorrhoeae* and *Neisseria meningitidis*. Most virulence factors present in one have an equivalent in the other,[18] providing at least one biologically plausible mechanism for cross-protection. In New Zealand, around 1 million individuals (81% of the population younger than 20 years) received almost 3 million doses of the OMV meningococcal B vaccine (MenZB)in a 2 year period,[19] providing an opportunity to assess this hypothesis.

In this case-control study, we assessed vaccine effectiveness of the 3+0 (ie, three primary doses with no booster) schedule of MeNZB that was used in New Zealand in 2004–08 among the population up to age

Research in context

Evidence before this study

WHO has reported that the global incidence of gonorrhoea is 100 per 100 000 per year, and multidrug-resistant strains have emerged. We searched PubMed for studies of gonorrhoea vaccine candidates published in English on or before Oct 30, 2016. We used the search terms "gonorrhoea" and "vaccine", with no date restrictions for primary studies. We identified four clinical studies—a whole-cell vaccine, a partly autolysed vaccine, a pilus, and a PorA vaccine—none of which affected acquisition of infection. However, we also found ecological data from national disease surveillance reports suggesting a decline in gonorrhoea in the period immediately after use of group B meningococcal outer membrane vesicle vaccines in Cuba, New Zealand, and, to an extent, Norway, suggesting that these vaccines could affect the incidence of gonorrhoea.

Added value of this study

Inoculation with the outer membrane vesicle meningococcal group B vaccine (MeNZB) seems to be associated with a significantly lower likelihood of contracting gonorrhoea compared with not being vaccinated. These findings provide experimental evidence that these vaccines could offer moderate cross-protection against a related organism, by an unknown mechanism of immunological protection. To our knowledge, our findings are the first showing a vaccine to have any effect against gonorrhoea. They also show for the first time, to our knowledge, that outer membrane vesicle vaccines can affect a mucosal infection.

Implications of all the available evidence

The potential ability of a vaccine to provide even moderate protection against gonorrhoea is of substantial public health interest, in view of the prevalence of gonorrhoea and the increase in antibiotic resistance. If the 4CMenB vaccine, which contains the New Zealand outer membrane vesicle vaccine, has a similar effect to MeNZB, then administering it in adolescent programmes could result in declines in gonorrhoea, as noted in New Zealand. The effect of outer membrane vesicle vaccines on gonorrhoea incidence suggests that research should be directed at identification of the antigens responsible for this finding. Our results provide a proof of principle that can inform prospective vaccine development not only for gonorrhoea vaccines but also for meningococcal vaccines.

20 years, against confirmed gonorrhoea cases between 2004 and 2016 in young adults aged 15–30 years.

Methods

Study design and data sources

We did a retrospective case-control study of data from sexual health clinics in New Zealand to estimate the vaccine effectiveness of MeNZB against gonorrhoea. Our study population consisted of all people aged 15–30 years (born between Jan 1, 1984, and Dec 31, 1998) attending participating sexual health clinics who were diagnosed with gonorrhoea or chlamydia, or both, and eligible to receive the MeNZB vaccine in New Zealand during a mass immunisation programme from July 19, 2004, to June 30, 2006 (aimed at infants aged 6 weeks to adults up to age 20 years), that was delivered through schools and primary care and available until 2008. The only contraindication to receiving the vaccine was a history of anaphylaxis to a previous dose or vaccine ingredient.

Data sources were the New Zealand National Health Index, which includes demographic information for anyone who has used the New Zealand health system, including data for ethnicity (priority coded Maori, Pacific Island, New Zealand European or other, and Asian), domicile, and level of deprivation by decile (in which 10 represents a meshblock in the most deprived 10% of areas and 1 a meshblock in the least deprived 10% of areas), and the National Immunisation Register, which includes all individuals who received MeNZB vaccinations from 2004. In New Zealand, everyone is assigned a unique person-specific alphanumeric identifier called a National Health Index Number, which is used across all health systems, including in these datasets, thereby enabling data linkage.

Sexual health clinics in New Zealand are self-referral clinics, and offer testing for opportunistic sexually transmitted infections (STIs) to sexually active attendees. We identified 35 sexual health clinics nationally. We did not approach 11 because of data issues, small catchment areas, restricted opening hours, or because these clinics had too few cases. We invited the remaining 24 clinics to participate in our trial.

Chlamydia and gonorrhoea are routinely tested for in both men and women in sexual health clinics. Gonorrhoea is commonly associated with chlamydia co-infection, and recommended treatment targets both infections.[20,21] Testing frequency reflects perceived STI risk, and people with ongoing risk are encouraged to test more often (eg, every 3–6 months). Sexual health clinics provided us with the National Health Index numbers associated with all chlamydia and gonorrhoea infections diagnosed from Jan 1, 2004, to Dec 31, 2016, for linkage to National Health Index and National Immunisation Register datasets. We used data linkage to assign vaccine exposure to cases and controls. We obtained ethical approval from New Zealand's Health and Disability Ethics Committee (15/CEN/189). Individual patient consent was not required because the data were anonymised beyond the clinic.

Procedures

During the study period, all sexual health clinics tested for gonorrhoea by culture or nucleic acid amplification

testing. Chlamydia was tested for by nucleic acid amplification testing. Each positive case was assigned a unique identifier for STI surveillance purposes. The number of cases and controls in any year by each sexual health clinic was validated against data reported to the national coordinating centre for STI surveillance. Patients with repeat diagnoses were included, but we only counted the first recorded diagnosis to avoid bias by contributing to an underestimation of CIs. People were considered to be vaccinated if they received three doses of vaccine at least 6 months before laboratory confirmation of gonorrhoea, because infection with gonorrhoea can be present months before diagnosis. People who received one or two doses at least 6 months before laboratory confirmation of gonorrhoea were judged to be partly vaccinated.

Statistical analyses

In our original protocol, we planned for three matched controls to each case. However, because we had sufficient numbers, we used all controls and adjusted for confounders in the analysis to provide greater statistical power. The recorded rate of chlamydia was nine times that of gonorrhoea in New Zealand in 2014 (629 cases per 100 000 people *vs* 70 cases per 100 000).[22] We calculated that a sample size of 1252 cases (ratio of controls to cases at least 3:1) would provide 80% power at an α of 0·05 for the largest range of possible vaccine effectiveness, including 20% or more, when coverage is up to 80%.[23] p values of less than 0·05 were deemed significant.

For our primary analysis, we considered cases to be those who were gonorrhoea-positive only and controls as chlamydia-positive only. Because co-infection could be assigned as either a control or a case, or as a separate disease state for both biological and epidemiological reasons, we did sensitivity analyses to establish how much a change in classification and inclusion of co-infected individuals would affect the estimate of vaccine effectiveness. Multivariate logistic regression including age group, ethnicity, sex, geographical location (based on the region served by the participating sexual health clinic), and deprivation quintile (based on data derived from the 2013 census) was used to provide an adjusted estimate of vaccine effectiveness. To estimate vaccine effectiveness for each sex, we ran the model—once with only men included, once with only women. Cases or controls with missing ethnicity or deprivation data were excluded. We estimated odds ratios (ORs) by conditional logistic regression, and then calculated vaccine effectiveness as a percentage—100×(1–OR).[24]

Further sensitivity analyses were done to explore two assumptions. First, there is lack of precision around time of infection, time to diagnosis, and when immunity might occur after vaccination. Therefore, we did three separate analyses with three different timepoints (1, 3, and 6 months) after the third dose of MeNZB at which we considered an individual immunised. Second, to estimate duration of vaccine effectiveness, we analysed the data grouped by time since vaccination, with cases and controls occurring in the years during and immediately after the vaccination programme in 2004–09 analysed separately from the distal cases and controls (ie 2010–14). We used SAS Enterprise Guide (version 6.1) for our analyses.

Role of the funding source

The study funder had no role in study design; data collection, analysis, or interpretation; or writing of the Article. The corresponding author had full access to all the data in the study and was responsible for the final decision to submit for publication.

Results

Of the 24 clinics we approached, 13 chose not to participate because of issues with data systems, low case numbers, staff shortages, or because they could not meet the research timelines. The remaining 11 clinics that participated represented nine district health boards in six diverse geographical regions covering 2 998 941 (64%) of the 4 680 666 people who make up the total New Zealand population.

Sexual health clinics provided details of 1759 confirmed incidences of gonorrhoea, 15 090 confirmed incidences of chlamydia, and 1329 incidences of confirmed chlamydia and gonorrhoea co-infection among 15 067 attendees (number of diagnoses exceeds the number of patients because of repeat infections; figure 1). The number of participants classified as partly vaccinated varied slightly depending on whether we set 6 months, 3 months (partial, n=967; unvaccinated, n=6282; vaccinated, n=7481), or 1 month (partial, n=972; unvaccinated, n=6237; vaccinated, n=7521) after vaccination as the point at which someone

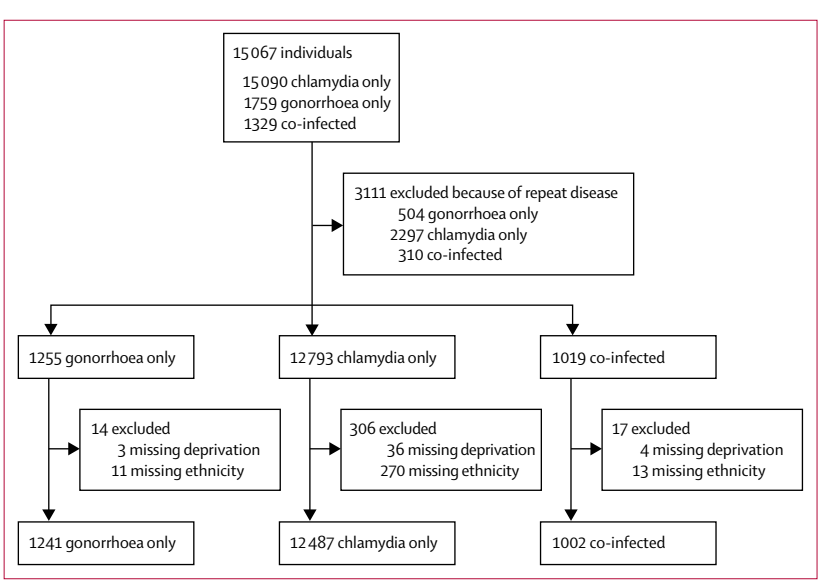

Figure 1: **Flow chart of participants, events, and inclusion in analyses**
The number of diagnoses exceeds the number of patients because of repeat infections.

	Gonorrhoea only (n=1241)	Controls	
		Co-infected (n=1002)	Chlamydia only (n=12 487)
Sex			
Female	483 (39%)	562 (56%)	7092 (57%)
Male	758 (61%)	440 (44%)	5395 (43%)
Ethnicity			
New Zealand European and other	516 (42%)	200 (20%)	5780 (46%)
Maori	467 (38%)	511 (51%)	4325 (35%)
Pacific Islanders	188 (15%)	262 (26%)	1870 (15%)
Asian	70 (6%)	29 (3%)	512 (4%)
Deprivation*			
1–2	101 (8%)	38 (4%)	1199 (10%)
3–4	125 (10%)	79 (8%)	1570 (13%)
5–6	207 (17%)	99 (10%)	2114 (17%)
7–8	298 (24%)	238 (24%)	3001 (24%)
9–10	510 (41%)	548 (55%)	4603 (37%)
Age group (years)			
15–19	441 (36%)	487 (49%)	5080 (41%)
20–24	613 (49%)	410 (41%)	5756 (46%)
25–30	187 (15%)	105 (10%)	1651 (13%)
Vaccination status			
Unvaccinated	632 (51%)	419 (42%)	5310 (43%)
Partial†	98 (8%)	89 (9%)	753 (6%)
Three doses	511 (41%)	494 (49%)	6424 (51%)

Data are n (%). *Deprivation is scored in deciles. A value of 10 suggests that a meshblock is in the most deprived 10% of areas in New Zealand.
†Partial vaccination means that people received at least one dose.

Table 1: **Demographic characteristics of participants**

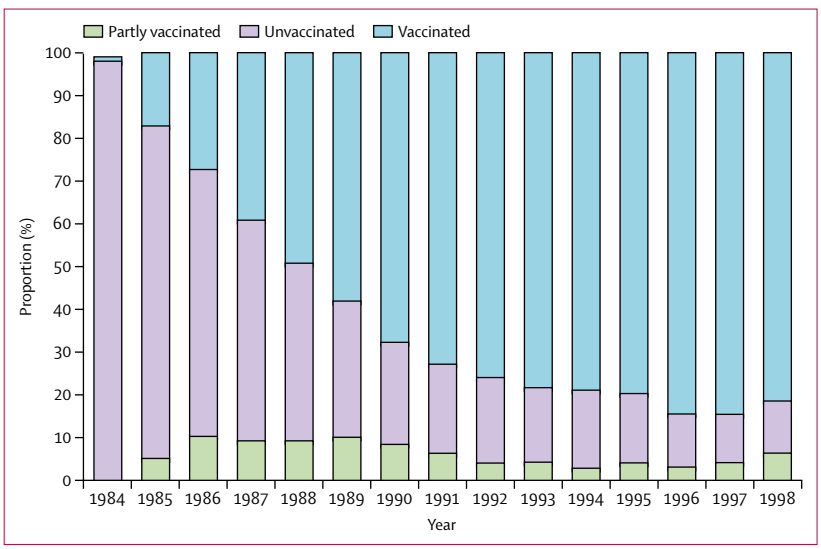

Figure 2: **Vaccination status of participants by year of birth**

was considered to be immunised. Maori and Pacific Island ethnicities had slightly higher probability of being co-infected with gonorrhoea and chlamydia than did Europeans or Asians (table 1). Too few participants who were partly vaccinated were available for analysis (table 1).

Vaccination coverage in the study of the national roll-out of MeNZB[25] was estimated as 86% for those aged 5–17 years (ie, people born in 1987–2001 who received three doses) and 54% for those born in 1984–86. Coverage in people born in 1984 or 1985 in our sample was lower (3–18%) than that estimated for the study population. Coverage in people born thereafter was similar to the estimated coverage (data not shown). The proportion of partly vaccinated individuals throughout the current study was less than 10%, particularly among younger participants (figure 2).

We included sex, ethnicity, deprivation, age group, and area as covariates in the final multivariable model. Interactions to test for effect modification between vaccination status and sex or ethnicity were not significant (data not shown). However, sex and ethnicity were retained in the model to adjust for confounding. The adjusted estimate for vaccine effectiveness of the MeNZB against confirmed cases of gonorrhoea among adolescents and adults aged 15–30 years was 31% (95% CI 21–39; p<0·0001). We could not measure a significant effect for partial vaccination, because of an absence of statistical power.

Estimated vaccine effectiveness in indigenous Maoris was 31% (95% CI 24–39), similar to that for the population as a whole. We had insufficient power to explore other ethnicities. Vaccine effectiveness was 36% (22–48) in women and 25% (11–36) in men, but the difference between sexes was not significant in our adjusted model. Shortening the length of time after the third vaccination after which a person was deemed to be fully vaccinated (from 6 months to 3 months and 1 month) decreased vaccine effectiveness slightly (to 29% [95% CI 20–38]), but not significantly, as shown by the large overlap of CIs (table 2).

Vaccine effectiveness remained significant, irrespective of whether co-infected people were included as controls (29% [95% CI 19–37]) or cases (23% [15–30]). Because co-infected people are likely to differ both epidemiologically and immunologically from mono-infected people, we assessed them separately against chlamydia-only controls, with gonorrhoea only cases removed. Vaccine effectiveness against co-infection was 14% (95% CI 1–26%).

When we analysed our sample as two separate groups according to time since vaccination, vaccine effectiveness in the years during and immediately after the vaccination programme (2004–09) was 20% (95% CI 2–34), compared with 9% (0–25) for 2010–14 (table 3). This trend of decreasing vaccine effectiveness over time was also evident when looking at the difference in the proportion of cases versus controls vaccinated by year (figure 3). Although adequately powered to detect a difference with the full sample, splitting the sample into two periods (2004–09 and 2010–14) reduced the power and accuracy of the estimate. Separation of the sample means that

years that have inconsistencies or are outliers have more leverage on the estimate. For example, numbers of cases and controls in 2004 and 2005 were low and the proportion of the cohort who would have been vaccinated and sexually active was also very low. The CIs for the split periods included the higher estimate for the combined sample. Despite this lack of power, the largest differences were in the years closest to when the vaccine was delivered (2008–09), when substantially more of the cohort would have been sexually active (figure 3). This effect reduced over time.

Discussion

In our New-Zealand-based case-control study, previous administration of the MeNZB vaccine in attendees to sexual health clinics was associated with a significant protective effect against gonorrhoea. This effect remained robust in multiple sensitivity analyses. Examination of time from vaccination to diagnosis suggested a waning of effect, although the decrease in effectiveness between 2004–09 and 2010–14 was not significant. Co-infection with chlamydia was associated with lower vaccine effectiveness. To our knowledge, ours is the first study to show an association between a vaccine and a reduction in the risk of gonorrhoea.

All individuals who received a dose of MeNZB were recorded in the National Immunisation Register, enabling population data linkage of MeNZB vaccination with confirmed cases of gonorrhoea and controls in the post-vaccination period via National Health Index numbers. We also had fairly complete ascertainment of cases. To explore the effect of assumptions on the effectiveness estimate, we used sensitivity analyses. Although vaccination exposure varied by year of birth, particularly in the youngest and oldest cohorts, we had sufficient observations in each category. Thus these variations probably had minimal effects.

We have minimised the potential bias of an observational study by including controls with another STI, chlamydia, diagnosed in publicly funded sexual health clinics routinely offering comprehensive STI testing. Primary care user fees in New Zealand are a recognised barrier to health care for low-income individuals,[26] which could bias attendance at free sexual health clinics towards higher deprivation. However, the MeNZB programme notably achieved social and ethnic equity in vaccine coverage.[25]

With respect to differences in attendance at sexual health clinics between vaccinated and unvaccinated people, those who received MeNZB might have been more likely to present for asymptomatic screening or more readily to present if symptomatic because receipt of the vaccination could suggest a more proactive willingness to seek health care. However, this behaviour should be consistent for case and control participants. Additionally, such behaviour would bias against vaccine effectiveness, because vaccinees would be more likely to seek care. Analysis of all STI cases from all health providers for the study period was not possible. Furthermore, such data would still have bias, because STI testing depends on access to health care.

Not all vaccinated individuals were at risk of gonorrhoea throughout the 11 year study period (2004–14). However, restriction of analyses by age group would have limited study power. Also, although younger participants probably had a lower risk of disease in the early part of the study (because of the minimal likelihood of sexual activity), our controls were those who had an STI associated with similar risk behaviour. We have adjusted for age group in our model, and thus we consider the bias to be minimal.

Our findings might not be generalisable to the general population. Not all people with gonorrhoea present to sexual health clinics—many people will consult their family doctor. Additionally, access to sexual health clinics is poor outside of New Zealand's large cities. Our study population of attendees at sexual health clinics might differ in age, ethnicity, socioeconomic variables, sexual behaviour, and past STI history from the general

	Crude OR (95% CI)	p value	Adjusted OR* (95% CI)	p value
Vaccination status†				
Vaccinated *vs* unvaccinated	0·67 (0·59–0·76)	<0·0001	0·69 (0·61–0·79)	<0·0001
Partial *vs* unvaccinated	1·09 (0·87–1·37)	0·44	1·09 (0·86–1·37)	0·49
Sex				
Female *vs* male	0·49 (0·43–0·55)	<0·0001	0·48 (0·42–0·54)	<0·0001
Ethnicity				
Asian *vs* European	1·53 (1·18–2·00)	0·0016	1·32 (1·01–1·74)	0·05
Maori *vs* European	1·21 (1·06–1·38)	0·0045	1·35 (1·17–1·56)	<0·0001
Pacific Islanders *vs* European	1·13 (0·95–1·34)	0·18	0·96 (0·79–1·16)	0·66
Deprivation				
1–2 *vs* 9–10	0·76 (0·61–0·95)	0·22	0·70 (0·56–0·89)	0·13
3–4 *vs* 9–10	0·72 (0·59–0·88)	0·04	0·67 (0·54–0·83)	0·02
5–6 *vs* 9–10	0·88 (0·75–1·05)	0·51	0·85 (0·71–1·01)	0·46
7–8 *vs* 9–10	0·90 (0·77–1·04)	0·32	0·85 (0·73–0·99)	0·39
Age group (years)				
15–19 *vs* 25–30	0·77 (0·64–0·92)	0·0004	1·10 (0·91–1·34)	0·49
20–24 *vs* 25–30	0·94 (0·79–1·12)	0·25	1·10 (0·92–1·32)	0·44
Location				
Region 1 *vs* region 6	0·81 (0·66–0·99)	<0·0001	0·81 (0·66–0·99)	0·0004
Region 2 *vs* region 6	0·78 (0·60–1·00)	0·01	0·80 (0·62–1·03)	0·02
Region 3 *vs* region 6	0·22 (0·14–0·39)	0·0001	0·23 (0·14–0·37)	<0·0001
Region 4 *vs* region 6	0·82 (0·64–1·06)	0·002	0·97 (0·75–1·27)	<0·0001
Region 5 *vs* region 6	0·54 (0·43–0·68)	0·05	0·51 (0·40–0·64)	0·001
Sensitivity analysis results				
Vaccinated *vs* unvaccinated‡	0·80 (0·73–0·88)	..	0·71 (0·62–0·80)	..
Vaccinated vs unvaccinated§	0·68 (0·60–0·77)	..	0·71 (0·62–0·80)	..

Gonorrhoea included only as cases, chlamydia included only as controls. The numbered regions represent the geographical areas of the sexual health clinics, but to protect privacy we are unable to identify them as per agreement with the clinics. OR=odds ratio. *Adjusted for ethnicity, sex, age group, deprivation, and geographical location. †Greater than 6 months between third dose and disease diagnosis. ‡Greater than 3 months between third dose and disease diagnosis. §Greater than 1 month between third dose and disease diagnosis.

Table 2: **Crude and adjusted ORs for gonorrhoea diagnosis**

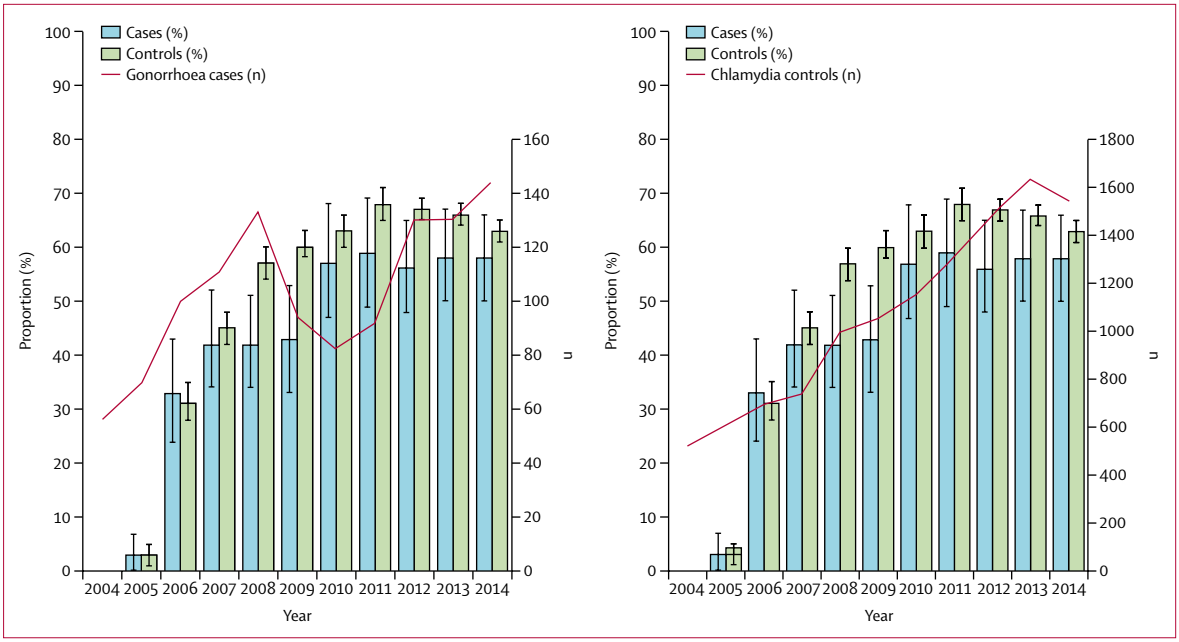

Figure 3: **Year-by-year difference in the proportion of cases and controls vaccinated and number of gonorrhoea (A) and chlamydia (B) diagnoses**
(A) and (B) are identical except for the gonorrhoea and chlamydia counts (note the difference in right axis scales). The difference in height between each pair of columns is the unadjusted estimate of the effect of the vaccine for each year. Error bars show 95% CIs. The number of cases of gonorrhoea and chlamydia gives an indication of the sample size (and by proxy the power) in the estimate for each year. The strongest measured effect occurred in the years immediately after the vaccination programme, then fell over time, suggest a possible waning of the vaccine effect.

	Crude OR (95% CI)	Adjusted OR* (95% CI)	Vaccine effectiveness (95% CI)
Cases have gonorrhoea, and controls have chlamydia (co-infected excluded)			
Vaccinated *vs* unvaccinated 2004–14	0·65 (0·57–0·72)	0·69 (0·61–0·79)	31% (21–39)
Vaccinated *vs* unvaccinated 2004–09	0·74 (0·61–0·89)	0·80 (0·66–0·98)	20% (2–34)
Vaccinated *vs* unvaccinated 2010–14	0·72 (0·61–0·86)	0·91 (0·75–1·11)	9% (0–25)
Cases have gonorrhoea, controls have chlamydia or are co-infected and have chlamydia			
Vaccinated *vs* unvaccinated 2004–14	0·67 (0·59–0·76)	0·71 (0·63 –0·81)	29% (19–37)
Vaccinated *vs* unvaccinated 2004–09	0·75 (0·62–0·90)	0·83 (0·68–1·02)	17% (0–32)
Vaccinated *vs* unvaccinated 2010–14	0·71 (0·60–0·85)	0·91 (0·75–1·12)	9% (0–25)
Cases have gonorrhoea or are co-infected, controls have chlamydia			
Vaccinated *vs* unvaccinated 2004–14	0·79 (0·72–0·87)	0·77 (0·70–0·85)	23% (15–30)
Vaccinated *vs* unvaccinated 2004–09	0·75 (0·65–0·87)	0·76 (0·65–0·89)	24% (11–35)
Vaccinated *vs* unvaccinated 2010–14	0·92 (0·81–1·05)	0·96 (0·84–1·14)	4% (0–16)
Cases are co-infected, controls have chlamydia only (gonorrhoea only excluded)			
Vaccinated *vs* unvaccinated 2004–14	0·98 (0·85–1·12)	0·86 (0·74–0·99)	14% (1–26)
Vaccinated *vs* unvaccinated 2004–09	0·78 (0·62–0·97)	0·69 (0·55–0·88)	31% (12–45)
Vaccinated *vs* unvaccinated 2010–14	1·21 (1·00–1·47)	1·03 (0·81–1·28)	0% (0–19)

OR=odds ratio. *Adjusted for ethnicity, sex, age group, deprivation, and geographical location.

Table 3: **Crude and adjusted ORs for gonorrhoea diagnosis excluding partly vaccinated participants**

population.[27] However, our study population is likely to be at higher risk for STIs and STI co-infection than the general population, which could have underestimated the possible effect of the vaccine in the wider population.

In view of the extensive variability among gonococcal strains and the variable homology between the *N gonorrhoeae* and *N meningitidis* species, the effect of the vaccine could vary in the presence of different strains. Identification of the strains of *N gonorrhoeae* captured around our study period will be important. Gonococcus and meningococcus are genetically homologous, sharing 80–90% of primary sequences. Most of the virulence factors in one species have an equivalent in the other.[18] Importantly, antigenic similarities between the species include several of the OMV proteins,[28] and homologous epitopes between OMV antigens and *N gonorrhoeae* should be researched further.

Gonorrhoea is primarily a mucosal infection, so whether OMV vaccines generate mucosal immunity, specifically IgA and T cells, is of interest. Although antibodies generated by OMV vaccination are mainly of the IgG isotype, IgM and IgA are also produced, albeit in lower concentrations. Antibody concentrations are short-lived but boost well. The human response to OMV vaccination is heterogeneous, and boosting broadens the subtype specificity.[29]

Natural immunity to meningococcal infection involves not only serum bactericidal activity but also mucosal and systemic memory T cells.[30] The mucosal T-cell immunity mainly involves T helper 1 cells, whereas the systemic response is more evenly balanced between T helper 1 and T helper 2 memory. In adults, a single dose of OMV vaccine induces T-cell memory that peaks after 6–7 days; the responses are not restricted to PorA but also include other surface proteins that could be shared with other group B strains.[31] OMV vaccination seems to selectively reprogramme naturally acquired immunity to

meningococcal disease at the mucosal surface, possibly via lipopolysaccharide in the vaccine and triggering of toll-like receptor signalling.[31] The MeNZB vaccine has shown effectiveness against all meningococcal disease,[19] suggesting a general adjuvant effect against homogeneous antigens via boosting and expansion of humoral and cellular immunity.

The duration of protection afforded by OMV vaccines against meningococcal disease varies by age and population, but serum bactericidal activity typically diminishes among a substantial proportion of vaccinees after 2 years.[32] The vaccine effectiveness of MeNZB against strains containing the same PorA subtype was estimated to be 68% for at least 3 years.[19] Our estimate of vaccine effectiveness against gonorrhoea fell as the time after vaccination increased. However, there is no reason to presume the effector mechanism is serum antibody only, and cellular immunity might have a role.

Varying our classification of co-infected individuals decreased vaccine effectiveness, but not significantly. However, analysis of co-infected individuals as a distinct group suggested that vaccine effectiveness is lower when gonorrhoea is complicated by chlamydia co-infection.

Co-infection with *Chlamydia trachomatis* and *N gonorrhoeae* is common.[33,34] Among our high-risk study population, nearly half of people with gonorrhoea were co-infected with chlamydia. Co-infection could favour the proliferation of gonococci,[35] effectively by providing them with more host cells. Co-infection has been associated with significant increases in concentrations of inflammatory cytokines (interleukins 1, 6, 8, and 10). Although cytokine concentrations are not increased in the genital secretions of women with gonorrhoea, serum interleukin concentrations are higher in infected women than in uninfected women. However, serum interleukin 1, 6, and 10 concentrations are significantly increased during concomitant infection with either *Trichomonas vaginalis* or *C trachomatis* in some women. Despite the systemic inflammation, concomitant infection is not associated with higher gonococcal antibody concentrations in either serum or genital secretions.[36] Co-infection seems to induce an immunological environment profoundly different from that present during infection with gonorrhoea alone, which could help to explain our finding that the vaccine seemed less effective in co-infected people.

MeNZB was developed to control an epidemic and is no longer available. However, the same OMV antigen in MeNZB has been included in a new vaccine that targets a broad range of group B *N meningitidis* and is now licensed in several countries. In addition to the New Zealand OMV vaccine, this new vaccine includes three recombinant proteins (NHBA, fHbp, and NadA) that are variably shared with *N gonorrhoeae,* although NadA is absent in all strains thus far studied and fHbp is not localised on the surface.[37,38] Based upon our results, assessment of this vaccine's potential effect on gonorrhoea infection seems warranted. Although an efficacy trial would be the gold standard, a before and after study in a population would be low cost and practical. Human challenge studies are also feasible, and could provide valuable additional information.

We noted an effect of a meningococcal group B OMV vaccine on a related organism with a very different mode of infection and clinical presentation that has thus far eluded efforts to develop an effective prophylactic vaccine. The potential ability of an OMV group B meningococcal vaccine to provide even modest protection against gonorrhoea would have substantial public health benefits in view of the prevalence of gonorrhoea. Modelling suggests that a vaccine with 30% efficacy could decrease the prevalence of gonorrhoea by more than 30% within 15 years, if immunity is maintained. Higher efficacy offering sustained protection results in greater reductions over a shorter period.[39] This potential benefit is of even greater importance in view of the increase in antibiotic resistance. Additionally, if some degree of cross protection is noted, then the findings can inform gonorrhoea vaccine development.

Contributors

HP-H was involved in the conception and design of the study, interpretation of results, and drafting of the Article. JP was involved in study design, led data management, did the analysis, and had roles in interpretation of results and revision of the Article. JM and PS were involved in study design, data acquisition, interpretation of results, and revision of the Article. BM was involved in data acquisition and revision of the Article. FG-S was involved in study design, interpretation of results, and revision of the Article. SB was involved in study conception, interpretation of results, and revision of the Article. All authors have seen and approved the final submitted version.

Declaration of interests

HP-H has been a consultant for GlaxoSmithKline, Merck, and Pfizer but has not received honoraria. SB has been a consultant for Novartis Vaccines, and is currently a consultant for GlaxoSmithKline, Protein Sciences, Merck, and WHO. All other authors declare no competing interests.

Acknowledgments

The study was supported by GSK Vaccines (formerly known as Novartis Vaccines and Diagnostics, which is now a member of the GSK group of companies after the acquisition by GSK of the non-influenza Novartis Vaccines division), and sponsored by Auckland UniServices. We sincerely thank all the participating sexual health clinics; Jill Sherwood, Selina Takanashi, and Ali Borman from the Institute of Environmental Science and Research for provision of laboratory-confirmed cases and controls; and Diana Lennon and everyone else involved in the development and implementation of the vaccination programme.

References

1 Newman L, Rowley J, Vander Hoorn S, et al. 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 EC. Gonococcal vaccines. *Clin Microbiol Rev* 1989; **2** (suppl)**:** S74–77.

3 Lewis DA. Global resistance of *Neisseria gonorrhoeae*: when theory becomes reality. *Curr Opin Infect Dis* 2014; **27:** 62–67.

4 Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. *N Engl J Med* 2012; **366:** 485–87.

5 Kirkcaldy RD, Harvey A, Papp JR, 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 JL, Jennings MP, Apicella MA, Seib KL. Is gonococcal disease preventable? The importance of understanding immunity and pathogenesis in vaccine development. *Crit Rev Microbiol* 2016; **2:** 928–41.

7 Mehta SD, Erbelding EJ, Zenilman JM, Rompalo AM. Gonorrhoea reinfection in heterosexual STD clinic attendees: longitudinal analysis of risks for first reinfection. *Sex Transm Infect* 2003; **79:** 124–28.

8 Eyre JH, Stewart B. The treatment of gononcoccus infections by vaccines. *Lancet* 1909; **174:** 76–81.

9 Greenberg I, Diena BB, Kenny CP, Znamirowski R. Preliminary studies on the development of a gonococcal vaccine. *Bull World Health Organ* 1971; **45:** 531–35.

10 Greenberg L, Diena BB, Ashton FA, et al. Gonococcal vaccine studies in Inuvik. *Can J Public Health* 1974; **65:** 29–33.

11 Boslego JW, Tramont EC, Chung RC, et al. Efficacy trial of a parenteral gonococcal pilus vaccine in men. *Vaccine* 1991; **9:** 154–62.

12 Zhu W, Chen C-J, Thomas CE, Anderson JE, Jerse AE, Sparling PF. Vaccines for gonorrhea: can we rise to the challenge? *Front Microbiol* 2011; **2:** 124.

13 Jerse AE, Bash MC, Russell MW. Vaccines against gonorrhea: Current status and future challenges. *Vaccine* 2014; **32:** 1579–87.

14 Pérez O, del Campo J, Cuello M, et al. Mucosal approaches in *Neisseria* vaccinology. *VacciMonitor* 2009; **18:** 53–55.

15 STI Surveillance Team. Sexually transmitted infections in New Zealand: annual surveillance report 2009. Wellington: Institute of Environmental Science and Research, 2010.

16 Whelan J, Kløvstad H, Haugen I, Holle M, Storsaeter J. Ecologic study of meningococcal b vaccine and *Neisseria gonorrhoeae* infection, Norway. *Emerg Infect Dis* 2016; **22:** 1137.

17 Holst J, Oster P, Arnold R, et al. Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV): lessons from past programs and implications for the future. *Hum Vaccin Immunother* 2013; **9:** 1241–53.

18 Tinsley CR, Nassif X. Analysis of the genetic differences between *Neisseria meningitidis* and *Neisseria gonorrhoeae*: Two closely related bacteria expressing two different pathogenicities. *Proc Natl Acad Sci USA* 1996; **93:** 11 109–14.

19 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:** 7100–06.

20 Wind CM, van der Loeff MFS, Unemo M, Schuurman R, van Dam AP, de Vries HJ. Time to clearance of *Chlamydia trachomatis* RNA and DNA after treatment in patients coinfected with *Neisseria gonorrhoeae*—a prospective cohort study. *BMC Infect Dis* 2016; **16:** 554.

21 Clarivet B, Picot E, Marchandin H, et al. Prevalence of *Chlamydia trachomatis, Neisseria gonorrhoeae* and *Mycoplasma genitalium* in asymptomatic patients under 30 years of age screened in a French sexually transmitted infections clinic. *Eur J Dermatol* 2014; **24:** 611–16.

22 Institute of Environmental Science and Research. Sexually transmitted infections in New Zealand: annual surveillance report 2014. Porirua: Institute of Environmental Science and Research, 2015.

23 Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions. New York: John Wiley & Sons; 2013.

24 Weinberg GA, Szilagyi PG. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. *J Infect Dis* 2010; **201:** 1607–10.

25 CBG Health Research Limited. Evaluation of the meningococcal B immunisation national roll-out. Final report. November, 2006. http://www.health.govt.nz/publication/evaluation-meningococcal-b-immunisation-national-roll-out-final-report (accessed June 28, 2017).

26 Barnett JR, Coyle P, Kearns RA. Holes in the safety net? Assessing the effects of targeted benefits upon the health care utilization of poor New Zealanders. *Health Soc Care Community* 2000; **8:** 159–71.

27 Manhart LE, Aral SO, Holmes KK, et al. Influence of study population on the identification of risk factors for sexually transmitted diseases using a case-control design: the example of gonorrhea. *Am J Epidemiol* 2004; **160:** 393–402.

28 Virji M. Pathogenic neisseriae: surface modulation, pathogenesis and infection control. *Nat Rev Microbiol* 2009; **7:** 274–86.

29 Rosenqvist E, Høiby EA, Wedege E, et al. Human antibody responses to meningococcal outer membrane antigens after three doses of the Norwegian group B meningococcal vaccine. *Infect Immun* 1995; **63:** 4642–52.

30 Davenport V, Guthrie T, Findlow J, Borrow R, Williams NA, Heyderman RS. Evidence for naturally acquired T cell mediated mucosal immunity to *Neisseria meningitidis*. *J Immunol* 2003; **171:** 4263–67.

31 Davenport V, Groves E, Horton RE, et al. Mucosal immunity in healthy adults after parenteral vaccination with outer-membrane vesicles from *Neisseria meningitidis* serogroup B. *J Infect Dis* 2008; **198:** 731–40.

32 Jackson C, Lennon D, Wong S, et al. Antibody persistence following MeNZB vaccination of adults and children and response to a fourth dose in toddlers. *Arch Dis Childhood* 2011; **96:** 744–51.

33 Bromhead C, Miller A, Jones M, Whiley D. Comparison of the cobas 4800 CT/NG test with culture for detecting *Neisseria gonorrhoeae* in genital and nongenital specimens in a low-prevalence population in New Zealand. *J Clin Microbiol* 2013; **51:** 1505–09.

34 Creighton S, Tenant-Flowers M, Taylor CB, Miller R, Low N. Co-infection with gonorrhoea and chlamydia: how much is there and what does it mean? *Int J STD AIDS* 2003; **14:** 109–13.

35 Vonck RA, Darville T, O'Connell CM, Jerse AE. Chlamydial infection increases gonococcal colonization in a novel murine coinfection model. *Infect Immun* 2011; **79:** 1566–77.

36 Hedges SR, Sibley DA, Mayo MS, Hook EW, Russell MW. Cytokine and antibody responses in women infected with *Neisseria gonorrhoeae*: effects of concomitant infections. *J Infect Dis* 1998; **178:** 742–51.

37 Comanducci M, Bambini S, Brunelli B, et al. NadA, a novel vaccine candidate of *Neisseria meningitidis*. *J Exper Med* 2002; **195:** 1445–54.

38 Hadad R, Jacobsson S, Pizza M, et al. Novel meningococcal 4CMenB vaccine antigens—prevalence and polymorphisms of the encoding genes in *Neisseria gonorrhoeae*. *APMIS* 2012; **120:** 750–60.

39 Craig AP, Gray RT, Edwards JL, et al. The potential impact of vaccination on the prevalence of gonorrhea. *Vaccine* 2015; **33:** 4520–25.