One vaccine, two diseases, three lessons

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Overview

Virtues of an outer membrane vesicle vaccine?

Kissing cousins, two divergent diseases

Serendipity and opportunity
Most meningococcal vaccines based on polysaccharide antigens (groups A, C, W135, Y)

Meningococcal Group B oligosaccharides cross react with fetal neuro tissue – not suitable vaccine antigen

Meningococcal Group B vaccine approaches needed to be different – non PS-Conjugate
There are many other antigenic structures aside from PS. **Outer-membrane vesicles** generate mainly strain specific responses against PorA which is highly variable across strains. Developed in 1980’s and used Cuba and Norway.
Meet the family

80-90% homology in primary sequences

High level of recombination

What is gonorrhea?
How common is gonorrhoea?

• Second most reported sexually transmitted disease in US (600,000 cases per annum)
• In NZ ~3000 cases per annum (60-90 per 100,000)
• To put in context
  – Invasive Pneumococcal Disease pre-vaccine <2s ~100 per 100,000
  – Meningococcal disease at its height 17 per 100,000
• Tairawhiti DHB 400 per 100,000
No correlate of protection and repeat infections

• Natural infection with gonorrhoea does not induce a protective immune response.
  – Repeated infection
• Spontaneous resolution
  – Weeks to months
• Over 100 years of effort but no vaccine
• Lucky penicillin came along...
Gonorrhoea resistance to antimicrobials is growing rapidly

X Sulfanilamide 1940s
X Penicillins 1980s
X Tetracyclines 1980s
X Fluoroquinolones 2007
X Extended spectrum cephalosporins (increasing)
• Multidrug resistant and extensively drug resistant

The recent emergence of the XDR gonococcal ‘superbug’ strongly argues the case for investment in research and development for both novel antimicrobial agents and, most importantly of all, a gonococcal vaccine.

Short list of epic fails

• Only 4 candidates advanced to clinical trials
  – Whole cell early 1900s
  – Partially autolyzed 1974
  – Pilus-based 1990s
  – Protein 1-based vaccine

• None worked

Challenges

• Appropriate infection models
• Variability of antigens
• Blocking of Ab to conserved antigens
• No correlate of protection, little natural immunity

Vaccine development will likely require the production of an immune response that is different to natural infection

In contrast

July 7 2017 – WHO call to action, situation has become desperate

Antibiotic-resistant gonorrhea on the rise, new drugs needed

Recent surveillance and research

Antimicrobial resistance is Neisseria gonorrhoeae: Global surveillance and a call for international collaborative action

More about gonorrhea

Antimicrobial resistance in Neisseria gonorrhoeae: Global surveillance and a call for international collaborative action

Antimicrobial resistance in Neisseria gonorrhoeae: Global surveillance and a call for international collaborative action

Antibiotic-resistant gonorrhea on the rise, new drugs needed
87 million

New gonorrhoea cases per year

Lesson one

Gonorrhoea is a disease in desperate want of a vaccine
NZ had an epidemic necessitating a tailor made Nm vaccine

Clone expressing the P1.7-2.4 PorA protein

OMV Vaccine based on Norwegian MenBvac (MeNZB™)

Partnership between the NIPH, (then) Chiron*, the University of Auckland, the Institute of Environmental Science and Research (ESR) and the WHO

*predecessor to Novartis Vaccines/Novartis Vaccines & Diagnostics AG


New Zealand MeNZB™

3+0 delivered 6 weeks apart
The MeNZB™ Programme sought to vaccinate NZers under 20 years

<table>
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<th>Phase I and II trials</th>
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<tr>
<td>Mass campaign to immunise population under 20 years in staggered roll out 3+0</td>
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<tr>
<td>0, 6, 12 weeks</td>
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<td>One million individuals vaccinated 2004-2006</td>
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<td>Coverage in children up to 15y ~80%, 15 – 17 y ~50%</td>
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<th>Infant National Immunisation Programme</th>
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<tr>
<td>Withdrawn</td>
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<td>no co-administration data PCV</td>
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<td>v. low uptake infants</td>
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Rayvin Ah Him, first infant to receive MeNZB, with NZ Prime Minister Helen Clark. NZ Herald
Impact of MeNZB™ was moderate

The epidemic had waned by the time the vaccine was developed and rolled out.

Vaccine Effectiveness (VE) of MeNZB™ was moderate

VE against strain-specific disease
- 73% (52–85%)\(^1\)
- 77% (62–85%)\(^2\) after mean 3.5 years
- 68%*

VE against non-epi group B
- 56% (17–77%)

VE against all meningococcal
- 67% (57–76%) against all meningococcal disease

*VE against invasive pneumococcal disease to measure residual confounding 56% (44–66%). Reduced the VE for group B to 68%.

What does this have to do with the clap?
Reported gonorrhoea in NZ


Reported chlamydia in NZ


Morbidity of *Neisseria* pathogenic species since 1970 in Cuba.


Several lines of indirect evidence suggest some degree of protection against gonorrhoea is possible following the administration of group B meningococcal vaccines.
Lesson two

Carpe diem
We did a case-control study using data-linkage

All adolescents and adults aged 15–30 years (born between 1984 and 1998) attending Sexual Health Clinics who were diagnosed with gonorrhoea, chlamydia or both, and eligible to receive the MeNZB™ vaccine in NZ from 2004–2008.
Cases and controls had similar risk factors including routine testing for both lab-confirmed gonorrhoea and chlamydia.

- Cases: 1241
- Co-infected: 12487
- Controls: 1002
VE and duration of protection
31% (95% CI 21–39%)

The difference in the bars represent vaccine effectiveness.
* = years where significant difference

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 Sacton, Barbara McArdie, 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 (MenNZB) 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 MenNZB, 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, 12 457 incidences of chlamydia, and 1062 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 MenNZB against gonorrhoea after adjustment for ethnicity, deprivation, geographical area, and sex was 31% (95% CI 21–39).

Interpretation Exposure to MenNZB 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 further vaccine development for this important public health problem.

The cohort study

Access to the data presented was managed by Statistics New Zealand under strict micro-data access protocols and in accordance with the security and confidentiality provisions of the Statistic Act 1975. Our findings are not Official Statistics. The opinions, findings, recommendations, and conclusions expressed are those of the authors, not Statistics NZ.
❖ Population NZrs eligible for the MeNZB vaccine who were born 1984-1999
❖ Excluded included immigrated, inactive, died
❖ Cases were hospitalized with a gonorrhea diagnosis only
❖ Analysis included sensitivity with less specific outcome codes
❖ Cox’s prop hazards models with Firth correction for rare outcomes
❖ VE 1-HR
The MeNZB vaccine was effective at preventing gonorrhoea related hospitalisations N=935,496

MeNZB had a child
Licensed vaccine: Bexsero

Composition of the Bexsero Vaccine
Estimate of vaccination impact was an Ng risk reduction of 59% (95% CI: –22% to 84%; P = 0.1).

During the same period, Chlamydia infections increased among persons of both age groups in the SLSJ region.
Summary of observational data
"A vaccine of moderate efficacy and duration could have a substantive effect if coverage is high and lasts over the highest risk period"

Fig. 1. The prevalence of gonorrhea in the absence of a vaccine, and with (A) vaccines of differing efficacies and 20 years duration of protection, or (B) vaccines with 100% efficacy and of differing durations of protection. Vaccine coverage is 100% of 13-year-olds.

Fig. 2. The prevalence of gonorrhea in the absence of a vaccine, and with different rates and types of vaccine coverage. (A) Vaccines have 100% efficacy and 20 years duration. (B) Vaccines have 50% efficacy and 20 years duration.
A vaccine would be good because gonorrhoea rates in NZ have nearly doubled in three years.
THIS IS WHERE
THE MAGIC HAPPENS
Opportunities to study interactions between MeNZB™ and gonococci

1. Sera from original MeNZB™ clinical trials
2. National collection of gonococcal isolates
3. Large MeNZB™ primed cohort (> 1 million)
4. Access to expired MeNZB™ stocks for pre-clinical studies
Cross-reactivity studies with mouse serum

Radcliff, O’Hanlon, Reynolds, Petousis-Harris
Cross-reactivity with MeNZB anti-sera and gonococcal OMVs – YES!

Radcliff, O’Hanlon, Reynolds, Petousis-Harris
BUT WHAT DOES IT ALL MEAN, BASIL?
We may have a useful gonorrhoea vaccine

- Factor H Binding Protein (fHbp)
- Neisserial adhesion A (NadA)
- Neisserial heparin binding antigen (NHBA)
- Neisserial GNA1030 and GNA2091 antigens
- NZ OMV

VACCINES FOR NEISSERIA GONORRHOEAE

Publication Classification

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U.S. Cl.
CPC ................ A61K 39/095 (2013.01); A61K 39/39 (2013.01); A61K 27/646 (2017.08)

ABSTRACT
Methods and compositions for immunizing a human subject against Neisseria gonorrhoeae.
Ann Jerse, Ph.D., of the Uniformed Services University of Health Sciences, is the principal investigator for the Gonorrhea Vaccine Cooperative Research Center (GVCRC), which will receive up to $10.7 million over five years....
Stimulated global strategy
Lesson three.

Don’t underestimate the difference you can make.

- This was a team of seven.
Acknowledgements

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For your enthusiasm, mentorship, support, and for leading the MeNZB adventure

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