MENINGOCOCCAL DISEASE IN NEW ZEALAND:

the science, the art and the denouement

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University of Auckland
DMID International Research in Infectious Diseases
Washington DC
May 2006
New Zealand Meningococcal Disease

Since 1991

>5000 cases
>200 deaths

[No outbreak cases ~ 500
deaths] ~ 25

Population ~ 4 million
New Zealand

Population ~ 4 million

- >14 years: 76%
- 0-14 yrs: 24%

Other 1%
Asian 6%
Pacific 9%
Maori 20%
European 64%

South Pacific
GNP NZ$7,734/capita

Other infectious diseases
- rheumatic fever
- bronchiolitis/pneumonia
- pertussis
- hepatitis B
- group A meningococcal disease 1985/1986
Regional Disease Burden in New Zealand
Meningococcal Disease Rates 2003
by Age Group and Ethnicity

Age (years)

Rate per 100,000

<1 1-4 5-9 10-14 15-19 20-29 30-39 40+

European
Maori
Pacific
Other

~ 80% disease
% of Total Case Numbers (<20s) by Ethnicity 1999-2003

- Māori: 37%
- NZ European: 36%
- Pacific: 24%
- Other: 9%
Meningococcal Case Strains (typed)  
1990 - 2004

Note: only includes cases for whom a specific strain type was identified
2005: 229 cases
Proportion of group B isolates with PorA P1.7b, 4 1991 – 2003
New Zealand Strain

- P1.7b, 4: 85.7%
- P1.7b, 4 variant: 0.6%
- P1 other: 13.7%
Capsular B polysaccharide is not immunogenic.

For serogroup B infections, bactericidal antibodies are directed against non-capsular surface antigens (i.e., OMP’s).

Strain-specific OMV vaccines are the only current response to group B epidemics.

New generation of B vaccines against all group B types are 5-10 years away.
### Group B Vaccine Developed for Outbreaks

<table>
<thead>
<tr>
<th>Country</th>
<th>Institution</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuba</td>
<td>Findlay Institute</td>
<td>P1.19,15</td>
</tr>
<tr>
<td>Norway</td>
<td>Norwegian Institute of Public Health</td>
<td>P1.7,16</td>
</tr>
<tr>
<td>Chile</td>
<td>Walter Reid, USA</td>
<td>P1.7(^b),3</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Norway/Chiron Vaccines</td>
<td>P1.7(^b),4</td>
</tr>
</tbody>
</table>
Meningococcal Vaccines Available

- Group A, C, W135, Y (polysaccharide or conjugate) for purchase

- Group B: unique development of Outer Membrane Vesicle (OMV) vaccine strain specific for New Zealand (MeNZB™) based on Norwegian “parent” OMV vaccine
Meningococcal Disease Group B

1991 →

1998 →

2000 →
Serum bactericidal antibodies have been shown to be the most important serologic correlate for vaccine efficacy.

- a functional assay using human complement
- also following disease and carriage

Goldschneider 1969
Gotschlich 1969 (Group A&C)
Milagres 1994 (Group B)
Jones 1998
Idanpaan-Heikkila 1995
Schematic Representation of Serum Bactericidal Activity (post dose 2) vs Vaccine Efficacy

- 22% (3-23 months)
- 45% (24-47 months)
- 52% (≥ 4 fold rise)
- 47% (≥ 4 fold rise)
- 74% (vaccine efficacy)

Moraes, Lancet 1992
Milagres, Inf Imm 1994
Bactericidal Assay after 3 doses of OMV Norwegian Vaccine: various target strains

Summary
Group B OMV Meningococcal Vaccines

- established efficacy in older age groups
- immunogenicity in infants (strain specific)
- immunogenicity (infants) is largely induced by class 1 Outer Membrane Protein (wild and genetically modified)

NIPH 1991 (Cuba & Norway)
Lancet 1992 (Brazil)
Vaccine 1995 (Chile)
JAMA 1998 (Infants)
Martin 2005
Problems In Evaluation Of OMV Vaccines In Small Children

- Inconsistently and incompletely evaluated
- Two doses rather than three doses
- Low rate of meningo disease confirmation
- Vaccine efficacy measured against meningo disease rather than vaccine/epidemic strain
- Case selection bias
- Natural decay of epidemic confounding VE evaluation

de Moraes 1992
Sierra 1991
Noronha 1995
Clinical Development Plan

Phase I
- ~75 adults

Phase II
- Randomised controlled trials (Immunogenicity and Safety)
- School children, toddlers, infants (n=900)
  - 2002/2003

PROVISIONAL LICENSURE (Medsafe)

Phase III/IV
- EPIDEMIC CONTROL
  - Intensified safety monitoring
  - Vaccine effectiveness by case-control
  - 2004/2005
Why Not A Randomised Controlled Trial?

- **Bactericidal Antibodies** indicate protection
- **Infants** produce strain specific antibodies
- **Strain-specific outbreak**
- **Immunogenicity** by age for licence
- Much RCT **safety** data (NIPH parent; Cuban OMV; Walter Reed in Chile)
- **Reactogenicity** – NZ trials
- **Manufacturing quality/physicochemical linkage** – NIBSC, UK
- **Provisional licensure** – public health emergency
Monitored Approach

- **Rapid clinical development** plan for epidemic control peer reviewed by individuals from:
  - CDC
  - FDA
  - UK
  - WHO
  - NZ reviewers

- Further **peer review** of individual aspects

- **Independent Safety Monitoring Board (ISMB)** set up for independent evaluation of safety and effectiveness data
Immunogenicity Trials
Immunogenicity Endpoints

Peer reviewed acceptable level for vaccine use for epidemic control.

8-12y, 16-24 mo, 6-8 mo
  • at least 60% responders (lower CI 50%)

6-12 weeks
  • at least 50% responders (lower CI 40%)
Serum Bactericidal Assay

SeroLogic correlate for vaccine efficacy
Functional assay using human complement

**IMMUNE RESPONSE**

≥ 4-fold rise in titre
compared to baseline

*Reaching at least 1:8
Standardised: Martin, Vaccine 2005

Goldschneider 1969
Gotschlich 1969 (Group A&C)
Milagres 1994 (Group B)
Aase 1995
Perkins 1998
Lehmann 1991, 1999
## Immunogenicity Trials 2002 - 2004

<table>
<thead>
<tr>
<th>Category</th>
<th>MeNZB™</th>
<th>Control Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>n = 25</td>
<td>Norwegian OMV</td>
</tr>
<tr>
<td>School</td>
<td>n = 485</td>
<td>Norwegian OMV</td>
</tr>
<tr>
<td>Toddlers</td>
<td>n = 231</td>
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<td>n = 201</td>
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</tr>
<tr>
<td>Young Infants*</td>
<td>n = 250</td>
<td>DTaP, IPV, Hib-HepB</td>
</tr>
</tbody>
</table>

- MeNZB™ vaccine 25µg
- 3 doses 0, 6, 12 weeks (0, 6, 14 weeks)*
- Observer blind RCT’s

Vaccine 2005; 23: 2191
Percentages of Sero-responders to vaccine strain NZ98/254 (B:4:P1.7b,4) as measured by serum bactericidal assay.
Percentages with SBA Titres $\geq 1:4$

to vaccine strain NZ98/254 (B:4:P1.7b,4)

### Table

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Baseline</th>
<th>Post Dose 2</th>
<th>Post Dose 3</th>
<th>Post Dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>n=24</td>
<td>n=23</td>
<td>n=23</td>
<td>n=23</td>
</tr>
<tr>
<td>8-12 years</td>
<td>n=236</td>
<td>n=230</td>
<td>n=230</td>
<td>n=230</td>
</tr>
<tr>
<td>16-24 months</td>
<td>n=260</td>
<td>n=254</td>
<td>n=255</td>
<td>n=255</td>
</tr>
<tr>
<td>6-8 months</td>
<td>n=223</td>
<td>n=219</td>
<td>n=239</td>
<td>n=239</td>
</tr>
<tr>
<td>6-10 weeks</td>
<td>n=239</td>
<td>n=45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Bar Chart

- **Baseline**
- **Post Dose 2**
- **Post Dose 3**
- **Post Dose 4**
## Geometric Mean SBA Titres
4-6 weeks post dose 3

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>GMT</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>23</td>
<td>51</td>
<td>(25-101)</td>
</tr>
<tr>
<td>8-12 years</td>
<td>230</td>
<td>25</td>
<td>(23-30)</td>
</tr>
<tr>
<td>16-24 months</td>
<td>255</td>
<td>16</td>
<td>(14-18)</td>
</tr>
<tr>
<td>6-8 months</td>
<td>219</td>
<td>17</td>
<td>(15-20)</td>
</tr>
<tr>
<td>6-10 weeks</td>
<td>239</td>
<td>8.65</td>
<td>(7.2-10)</td>
</tr>
</tbody>
</table>
Safety and Reactogenicity
Local Reactogenicity of any severity, after at least one dose of NZ Meningococcal B vaccine

- Erythema: 40% (Adults), 30% (8-12 years), 25% (16-24 months), 30% (6-8 months)
- Swelling: 20% (Adults), 15% (8-12 years), 10% (16-24 months), 15% (6-8 months)
- Induration: 30% (Adults), 25% (8-12 years), 20% (16-24 months), 25% (6-8 months)
- Tenderness: 90% (Adults), 85% (8-12 years), 80% (16-24 months), 85% (6-8 months)
Key Elements for Control of Meningococcal B Epidemic

- Well characterised strain-specific epidemic
- Standardised laboratory assay
- Vaccine technology transfer & scale-up production
- Physico-chemical linkage of “parent” vaccine to MeNZB™
- Clinical trials
- Provisional licence (New Zealand Medsafe)
- Post-licence - safety monitoring
  - vaccine effectiveness evaluation
- Immunisation register
- Funding and engagement

JID 1998; 177: 497
NZMJ 2004; 117: 1015
Vaccine 2005; 23: 2231
Vaccine 2005; 23: 2197
Licence\(^+\) MeNZB™ for Epidemic Control

- **July 2004**: 6 mo – 19 yr children (Sth Auckland)
- **February 2005**: 6 wk – 6 mos\(^+\)
- **May 2005**: All ages, all NZ

**SEQUENTIAL DELIVERY**

+ Auckland only
### First Stage of MeNZB™ Delivery

**South Auckland Coverage: Age at First Dose Tracking**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Maori</th>
<th>Pacific</th>
<th>Other</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 wks – 11 months</td>
<td>64%</td>
<td>73%</td>
<td>80%</td>
<td>73%</td>
</tr>
<tr>
<td>1 – 4 years</td>
<td>81%</td>
<td>87%</td>
<td>94%</td>
<td>88%</td>
</tr>
<tr>
<td>5 – 17 years</td>
<td>91%</td>
<td>92%</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td>18 – 19 years</td>
<td>60%</td>
<td>67%</td>
<td>83%</td>
<td>75%</td>
</tr>
<tr>
<td>0 – 19 years</td>
<td>85%</td>
<td>88%</td>
<td>93%</td>
<td>89%</td>
</tr>
</tbody>
</table>

CMDHB + EC Population ~ 150,000

NZ Ministry of Health 27 November 2005

- Passive surveillance (general practitioners)
- Hospital Monitoring: rare and all event
- Background disease rates
- Data Base matching
- Independent Safety Monitoring Board until June 2006
### Meningococcal Carriage Pre-vaccination, Auckland

(n= 77)

#### By Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Positive Isolates</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15y</td>
<td>7/48</td>
<td>(14.6%)</td>
</tr>
<tr>
<td>16y</td>
<td>67/532</td>
<td>(12.6%)</td>
</tr>
<tr>
<td>≥ 17y</td>
<td>3/60</td>
<td>(5.0%)</td>
</tr>
</tbody>
</table>

#### By Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Positive Isolates</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacific</td>
<td>41/207</td>
<td>(19.8%)</td>
</tr>
<tr>
<td>Maori</td>
<td>10/60</td>
<td>(16.7%)</td>
</tr>
<tr>
<td>European</td>
<td>18/225</td>
<td>(8.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>8/141</td>
<td>(5.7%)</td>
</tr>
</tbody>
</table>

P1.4 Positive Isolates = 9 (1.4%)
In the absence of a randomised controlled trial+ for **EFFECTIVENESS** descriptive methods are in place.

+70,000 children, including a control group receiving placebo, run over 2 years
Vaccine Effectiveness
Evaluation Methods

POISSON REGRESSION MODEL:
programme effectiveness

CASE-CONTROL STUDY:
vaccine efficacy (B and P1.4 cases only)

SURVEILLANCE

Ameratunga et al Vaccine 2005; 23: 2231
NZ Vaccine Strain Meningococcal Cases 2001-2005 (6w-19y)
Epidemic Strain Meningococcal Cases in South Auckland* (6w-19y) and Vaccine (3 doses) Coverage

- Fully vaccinated
- Unvaccinated/partially vaccinated
- % coverage

NZ Ministry of Health
*CMDHB + EC
VACCINE Vaccine 6w-6m
Meningococcal Management Team

Diana Lennon+ Professor of Population Child & Youth Health
Principal Investigator, (Trials & Effectiveness), University of Auckland

Jane O’Hallahan+ MVS Director, Ministry of Health
Philipp Oster+ Chiron Vaccines

Professional Advisors*
Ingeborg Aaberg Norwegian Institute of Public Health
Diana Martin Principal Scientist, ESR
Kim Mulholland University of Melbourne
Liane Penney Massey University
Teuila Percival Kidzfirst Hospital, Auckland
Stewart Reid General Practitioner
Joanna Stewart Statistician, University of Auckland

FUNDERS
Ministry of Health
Chiron Vaccines

* alphabetical order

Norwegian Institute of Public Health
Ministry of Health
University of Auckland
Chiron Vaccines
University of Auckland Team Leaders

Phase I: Vanessa Thornton
Phase II: School: Kumanan Rasanathan
                Jamie Hosking,
                Flo Chan-Mow
                Toddlers: Sharon Wong
                Infants: Vili Sotutu
                Young Infants: Sharon Wong
                Extension Studies: Jackie Yan
                Carriage: Kura Horsfall
                Case Control: Alex Macmillan
                Vaccine Breakthrough: Kura Horsfall
                Statistician: Joanna Stewart
                Laboratory: Diana Martin & Team
                Principal Investigator: Diana Lennon

Vaccine Effectiveness Team

University of Auckland: (Case Control)
Diana Lennon Joanna Stewart
Alex Macmillan David Scott
Shanthi Ameratunga

Auckland Regional Public Health: (Case Control)
Cathy Pikholz Nick Jones
Will Patterson Bronwyn Thompson
Aumea Herman

Data Management Group Ministry of Health:
Yvonne Galloway Anne McNicholas
Paul Stehr-Green Jane O’Hallahan

Acknowledgements
Trial participants and families
Many research, study, Plunket & public health nurses
Schools
Community Advisory Boards
Many community health workers
ESR Team
Rare events to be monitored

- Anaphylaxis
- Encephalopathy/encephalitis
- Flaccid paralysis
- Thrombocytopenia
- HHE
- Seizures
- Petechial rashes
- catch all categories e.g. all intensive care admissions within 7 days/ unusual events thought to be related to immunisation/Deaths - SIDS
Major serotype of group B invasive meningococcal disease amongst the contributing countries, 1999-2002

<table>
<thead>
<tr>
<th>Major serotype</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>B:15;P1.7, P.16</td>
<td>Austria, Denmark, France (with B:4; P1.4)</td>
<td>Austria, Denmark, Germany, Italy, Norway</td>
<td>Austria, Denmark, Germany, Italy</td>
<td>Austria, Denmark</td>
</tr>
<tr>
<td>B:4; P1.4</td>
<td>Belgium, England &amp; Wales, Finland, France (with B:15; P1.7, P.16), Greece, Ireland, Italy, Netherlands</td>
<td>Belgium, England &amp; Wales, Finland, Greece, Ireland, Netherlands</td>
<td>Belgium, England &amp; Wales, Finland, Greece, Ireland, Netherlands, Norway</td>
<td>Belgium, England &amp; Wales, France, Germany, Greece, Ireland, Netherlands, Switzerland</td>
</tr>
<tr>
<td>B:4:1.15</td>
<td>Malta, Spain</td>
<td>Malta, Spain</td>
<td>Malta, Spain</td>
<td>Czech Republic, Finland, Malta, Spain</td>
</tr>
</tbody>
</table>

http://www.euibis.org/meningo/n_meningitidis_network.htm
Distribution of serogroups - all age groups, USA and EU (1999-2000)

Noah and Henderson, 1999-2000
Immunoblot showing responses to MeNZB™

D Martin
Serum Bactericidal Assay

Serologic correlate for vaccine efficacy*
Functional assay using human complement

**IMMUNE RESPONSE**
≥ 4-fold rise in titre
compared to baseline*

*Goldschneider 1969
*Gotschlich 1969 (Group A&C)
*Milagres 1994 (Group B)
*Reaching at least 1:8
Immunogenicity Trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Group</th>
<th>MeNZB™</th>
<th>Control Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Adults</td>
<td>n = 25</td>
<td>Norwegian OMV</td>
</tr>
<tr>
<td>II</td>
<td>School</td>
<td>n = 485</td>
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- MeNZB™ vaccine 25μg
- 3 doses 0, 6, 12 weeks
  (0, 6, 14 weeks)*
- Observer blind RCT’s
### New Zealand Immunisation Coverage Summary 2005

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Fully Vaccinated at 2 years</th>
<th>at 2-3 yrs</th>
<th>Catch-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maori</td>
<td>69%</td>
<td>78%</td>
<td>9%</td>
</tr>
<tr>
<td>Pacific</td>
<td>85%</td>
<td>88%</td>
<td>3%</td>
</tr>
<tr>
<td>Asian</td>
<td>80%</td>
<td>83%</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>80%</td>
<td>84%</td>
<td>4%</td>
</tr>
</tbody>
</table>
New Zealand: Fully Vaccinated at 2 years

<table>
<thead>
<tr>
<th>Year</th>
<th>All</th>
<th>Maori</th>
<th>Pacific</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991°</td>
<td>56%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995/1996⁺</td>
<td>72%</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>2005°</td>
<td>77.5%</td>
<td>69%</td>
<td>82%</td>
</tr>
</tbody>
</table>

⁺ North Health
° National Coverage Survey (cluster methodology)