Meningococcal Disease Ascendant: how should Australia respond?

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PHAA National Immunisation Conference 2018

Declaration of conflicts of interest

- Membership of Immunisation committees
  - Australian Technical Advisory Group on Immunisation, 2005-14
  - Chair, ATAGI Meningococcal & Hib Working Parties, 2002, 2006 – present
  - Chair, WA Vaccine Safety Advisory Committee, 2011 - present
- Vaccine Scientific Advisory Groups
  - GlaxoSmithKline - Pertussis, pneumococcal protein vaccines, maternal immunisation
  - Pfizer - Meningococcal vaccines
  - Janssen – Bacterial vaccines
  - Sanofi – influenza vaccine
  - Baxter – Meningococcal C conjugate vaccine
  - MCRI - Rotavirus RV3 DSMB Chair
  - No personal remuneration
- Vaccine Research
  - Principal Investigator of industry sponsored multi-centre studies for Baxter, CSL, GSK, Medimmune, Merck, Pfizer, Sanofi, Novartis
  - Travel support to present at scientific conferences
    - Sanofi, Pfizer, Baxter, GSK
  - Research funding for Investigator initiated studies
    - GSK, Merck, Novartis
- Views expressed during this presentation are mine only

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Talk Outline

- Changing epidemiology in Australia
- Understanding meningococcal disease and immunity
- Response to rise in serogroup W disease
- Overseas experience
- Program Options for Australia
- Long-term control strategies for serogroup B disease

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Learning from the Past
Issues for MCC vaccines in Australia PHAA 2002

- Priority compared to other vaccines
- public health versus political/public priority
- Implementation issues
  - fitting into current immunisation schedules
  - state based versus national program
  - cost effectiveness

- Options
  - available on private market only
- mass immunisation campaign
  - very expensive & need to include young adults
- infant immunisation campaign
  - 3 doses more expensive
  - low incidence of disease under 1 year
- single dose MCC at 12 months
  - more cost effective & should provide long term protection
- adolescent campaign
  - 15 year olds : start of increased risk
  - catch up to 17 years
  - What about young adults?
  - Herd effects?

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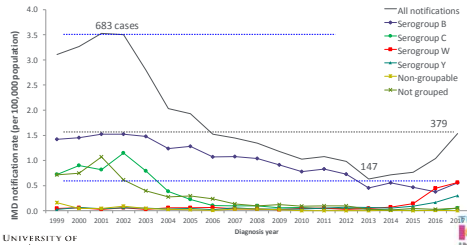
Meningococcal notification rate by serogroup and year, 1999–2017



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Source NNDSS with thanks Cyra Patel

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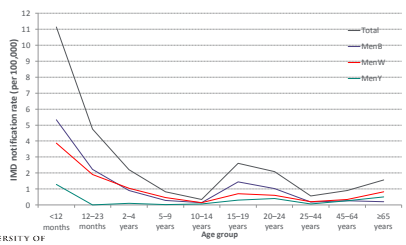
Meningococcal disease notification rate by serogroup and age group 2016–2017



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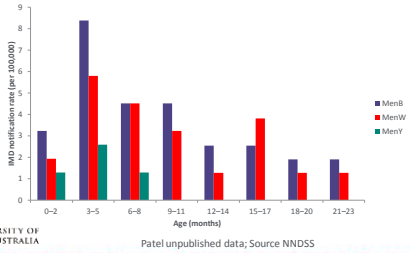
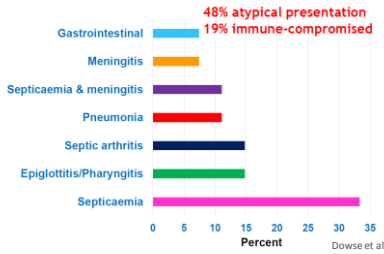
Meningococcal notification rates in <2 years, 2016–17



Patel unpublished data; Source NNDSS

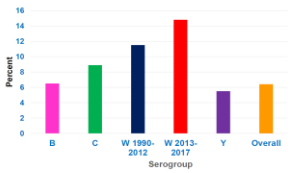
Meningococcal W presentations in WA 2013 - 2017



Dowse et al CDNA 2017

Meningococcal Disease Case fatality rates by serogroup,

WA 1990 – 2017



Increase in Endemic *Neisseria meningitidis* Capsular Group W Sequence Type 11 Complex Associated With Severe Invasive Disease in England and Wales

Australia 2016–2017

Serogroup	Number of deaths	Number of cases	Case Fatality Ratio
MenB	10	229	4.4%
MenW	23	247	9.3%
MenY	5	114	4.4%

Hypervirulent W:2a:1.5,2:ST11 South American clonal complex also seen in UK with high case fatality rate and atypical clinical presentations

MenACWY Vaccination Options

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Development of effective Meningococcal conjugate vaccines

- US Army studies defined serologic correlate of natural protection (1960s) – hSBA* titre ≥1:4
- Men C capsular PS antibodies protective
- Polysaccharide vaccines provided short-term protection in individuals >2 years but antibody low avidity and lacked bactericidal activity in infants
- Conjugate vaccines recruit T cell help, efficacious in infants and induce memory and production of high avidity antibody
- UK population studies have defined a MenC conjugate vaccine correlate of protection (VE studies, 2000s) - rSBA† titre ≥1:8
  - Similar correlate expected for serogroups W and Y though much debate

*Serum bactericidal assay using human complement source
†Serum bactericidal assay using baby rabbit complement source

Meningococcal Conjugate vaccines

- Meningococcal C conjugate vaccines
  - Licensed for all age groups; MenC-CRM; MenC-TT; highly effective with herd impact
- HibMenC-TT
  - Previously on NIP for toddlers in Australia;
- MenA-TT
  - Vaccine for Meningitis belt in Africa with successful mass immunisation campaigns
- MenACW$_{135}$Y conjugate vaccines
  - MenACWY-TT (Nimenrix™; Pfizer) : approved for use as single dose in toddlers on NIP
  - MenACWY-CRM$_{197}$ (Menveo™; GSK)
  - MenACWY-DT (Menactra™; Sanofi)
  - Licensed for infants, toddlers, children & adults in Australia
  - Used as adolescent booster routinely in UK, Canada, USA
  - Used for infant immunisation in at risk groups
  - State based programs in Australia from 2017 with use in multiple outbreaks predominantly ATSI populations in central & western Australia

Reactogenicity of MenACWY conjugate vaccines

- Safe and well tolerated similar to Men C & HibMenC conjugate vaccines
- Local reactions, fever, drowsiness in young children
- Local pain, headaches, reduced appetite, chills more commonly reported in adolescents / young adults
- No increased of allergic reactions
- No evidence of an association with Guillain-Barré syndrome in adolescents
- Can be given safely with routine NIP vaccines as well as at same time as Bexsero (A Leeb PHAA 2018)

MenACWY conjugate vaccine recommendations

Registered vaccination schedules for 4vMenCVs by age group for healthy children & adolescents

Age at commencement of vaccine course	Brands registered for use in Australia	Number of doses required	Recommended interval between doses
2–6 months	Menveo	4*	8 weeks between the first 3 doses
7–11 months	Menveo	2	8 weeks
12–23 months	Menveo OR	2	8 weeks
	Nimenrix	1	Not applicable
≥2 years‡	Menactra, Menveo or Nimenrix	1	Not applicable

* 2+1 schedules also recommended in some EU countries

MenACWY vaccines for adolescents

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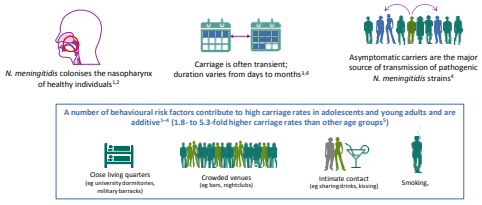
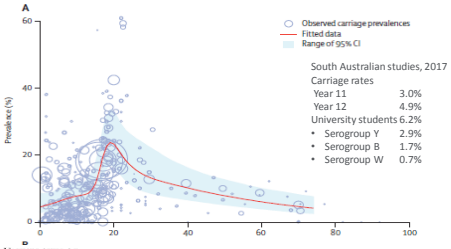
Asymptomatic carriage of *N. meningitidis* is common in healthy individuals, and is the major source of disease transmission



1. Christensen H *et al. Lancet Infect Dis* 2010;10:853–861; 2. Vetter V *et al. Expert Rev Vaccines* 2016;15:641–658; 3. Mueller JE *et al. Emerg Infect Dis* 2007;13:847–854; 4. Yazdankhah SP *et al. J Med Microbiol* 2004;53:821–832

Meningococcal Carriage prevalence is highest in young adults



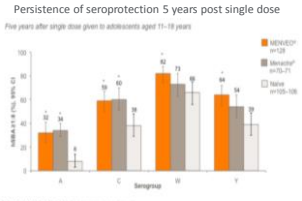
Christensen H. Lancet Infectious Diseases 2010;10(12):853-61. Epub 2010/11/16. doi: 10.1016/S1473-3099(10)70251-6

Marshall McMillan PHAA 2018

MenACWY vaccines are Immunogenic in Adolescents

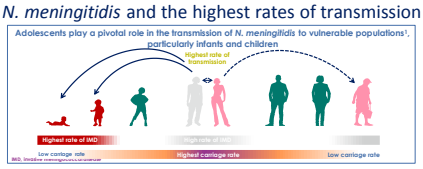
- All MenACWY conjugate vaccines are immunogenic after a single dose
- Some differences in seroprotection and seroconversion rates but variable between studies & assays
- Importantly antibody persistence maintained up to 5 years

Persistence of seroprotection 5 years post single dose



Baxter 2014

Adolescents and young adults have the highest carriage rates of *N. meningitidis* and the highest rates of transmission

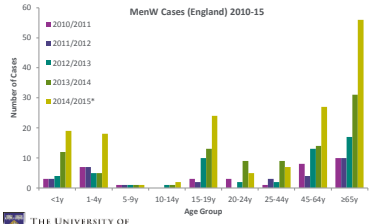


State Adolescent vaccination programs: Meningococcal ACWY[2]

- Young people aged 15 to 19 years as a single dose
  - Provides direct protection and reduce carriage for herd effects
  - Year 10 to 12 students in schools : coverage estimates ranging from 65 – 75%
  - Young adults in university health centres (university students) or from a GP: lower coverage 20 – 30%
- How long will herd effects take if start in Year 10?

1. Vetter V et al. Expert Rev Vaccines 2016;15:641–658;
2. http://www.healthywa.wa.gov.au/Articles/J_M/Meningococcal-vaccine

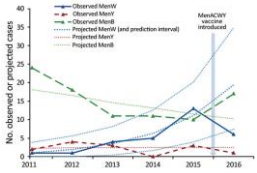
Overseas approach to rising MenW disease: UK



- Wide age range affected
  - Incidence highest in infants and adolescents but still high number of cases in older adults
- Modelling to estimate 2x & 4x increase in cases
- Vaccinating adolescent cohorts simultaneously in catch up to accelerate control: ~4x faster

JCVI MenACWY recommendations: February 2015

- Even JCVI considered a public health emergency despite low no. of cases
  - rapid increase in virulent MenW
  - international experience (e.g. South America)
- Recommended MenACWY programme in adolescents with catch up to 19 years
  - 2nd highest incidence group
  - Excellent protection expected after a single dose cf infants
- Importance of quick catch-up to generate herd protection across age range & slow the rate of increase
- Limited impact on unvaccinated cohorts to date



Campbell et al Emerg Infect Dis 2017;23:1184-87.

MenACWY-DT Effectiveness in USA 2006 - 2013

- Menactra (MenACWY-DT) recommended for adolescents in USA in 2005 due to C & Y cases
- Recommendation for 11-18 years with preferred age 11-12 years
- Early effectiveness estimates 80-85%
- Case control study to evaluate effectiveness of adolescents offered single dose at 11–12 years in CDC ABC and Meningnet sites.
- 181 Cases (20% vaccinated) and 199 Controls (44% vaccinated)
- Moderate efficacy with possible evidence of waning immunity
- ACIP recommendation for 2nd dose at 16 years

	Vaccine Effectiveness	95% Confidence Interval
MenACWY serogroups	69%	51% - 80%
Serogroup C	77%	57% - 88%
Serogroup Y	51%	1% - 76%
Duration		
<1 year	79%	49% - 91%
1 - <3 years	69%	44% – 83%
3 – 7 years	61%	25% - 79%

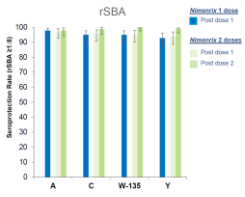
Cohn et al. Pediatrics 2017;139:e20162193

Adolescent MenACWY program for NIP

- 3 potentially suitable licensed vaccines
- Limited information on impact on carriage
- PBAC review MenACWY-TT March 2018
  - Some concerns regarding impact of natural immunity
  - cost-effectiveness of the MenACWY-TT vaccine uncertain
  - requirement to translate serological outcomes to clinical outcomes
  - assumed extent of herd immunity was a key driver of the result
  - recommended the NIP listing contingent upon a price reduction so incremental cost-effectiveness ratio is <$15,000 per QALY gained
- Implication for future PBAC submissions
- Importance of impact on carriage in Australian context

MenACWY vaccines for toddlers

Immunogenicity of MenACWY-TT in toddlers



- No impact of concomitant administration with PCV13 on SBA or PCV responses or safety
- hSBA seroprotective responses in subset to lower for W and Y (63 -67%)
- Approved by PBAC March 2018: "*considered the MenACWY-TT vaccine would be acceptably cost-effective if subsidised on a cost-minimisation basis with the MenC component of the Hib-MenC vaccine (Menitorix).*"

Cutland et al Vaccine 2018; 14:1908-16

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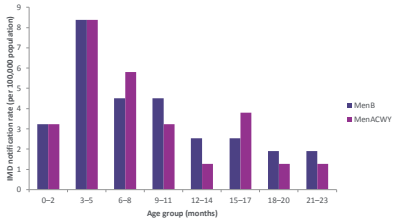
Meningococcal disease in under 2 years, 2016–17



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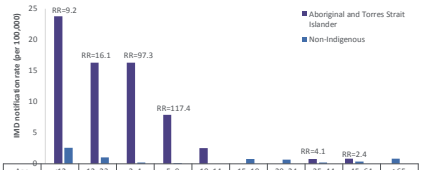
MenW notification rate for Aboriginal and Torres Strait Islanders by age group, 2016–2017: need for infant & childhood program?



Age group	<12 months	12–23 months	2–4 years	5–9 years	10–14 years	15–19 years	20–24 years	25–44 years	45–64 years	≥65 years
Aboriginal & TSI	9	6	17	13	4	0	0	3	2	0
Non-indigenous	15	6	3	2	0	21	21	25	39	61

Patel PHAA 2018

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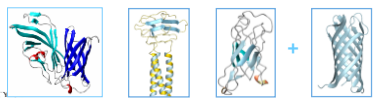
Meningococcal B Vaccines – a long-term solution

West Australian 21 May 2016

Rationale for a Multicomponent Serogroup B Vaccine (4CMenB; Bexsero™)

- Target multiple factors that are important for meningococci survival, fitness, or virulence
  - Broad coverage of globally representative strains
  - Protect against known hypervirulent epidemic strains
  - Limits potential for emergence of escape mutants
  - Potential for synergistic bactericidal activities and improved persistence of immunity with multiple target antigens



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MenB Vaccine Effectiveness in UK with 2+1 schedule

- Commenced infant MenB program in Sept 2015 under 2-4-12 month schedule
- Strong public support for program
- Rapidly achieved high coverage of over 90% (>1 million doses given)
- No major safety concerns with use of prophylactic paracetamol
- 2-4-fold increase in presentations to GPs / EDs for fever
- Effectiveness demonstrated after 2 doses (no effect of 1 dose)

Doses	Cases vaccinated / total	Average matched coverage	VE (95 %CI)
2+0	9/13 (69%)	92.9%	82.9% (24.1% to 95.2%)

Assuming 88% of MenB strains covered by 4CMenB, then VE against vaccine-preventable strains ~94%

Ladhani Lancet 2016

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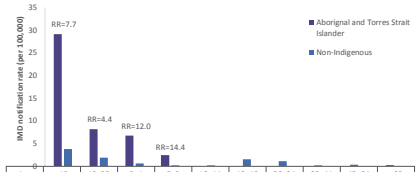
Meningococcal B notification rate for Aboriginal and Torres Strait Islanders vs non-Indigenous people, by age group, 2016–2017



Age group	<12 months	12–23 months	2–4 years	5–9 years	10–14 years	15–19 years	20–24 years	25–44 years	45–64 years	≥65 years
Aboriginal & TSI	11	3	7	4	0	0	0	0	0	0
Non-Indigenous	22	11	10	5	4	43	35	26	32	16

Meningococcal B vaccines for infants and young children

- UK experience provides additional certainty on safety and effectiveness of 4CMenB vaccine under 2+1 schedule
- High level of public demand and coverage
- Cost-effectiveness of multi-dose schedule remains major barrier to NIP listing
- High rates of MenB disease in ATSI children provide compelling case for targeted program ASAP
- Will state based program provide the political impetus for managed entry

MenB Vaccines for adolescents and young adults

- Two licensed vaccines for adolescents and young adults
  - Bexsero™ : 4 component protein vaccine
  - Trumenba™: Factor H binding protein (2 Families)
  - Both vaccines provide broad protection against diverse MenB isolates as measured by SBA after 2 dose schedules
  - Both are safe and well tolerated
- Impact on carriage not yet known but critical for cost effectiveness estimates
  - Importance of B part of it SA carriage study
  - Potential for cross protection against gonorrhoea (J. Paynter NZ experience Thursday)

Meningococcal Vaccine Summary

- The emergence of Meningococcal W_{135} strain in Australia has led to increased public & provider concern though relatively low incidence
- MenAWCY conjugate vaccines are safe and immunogenic at all ages
- Adolescent MenACWY program will provide direct protection and may lead to herd immunity as program matures
- Toddler program will provide direct protection for young children but immunity likely to wane
- ATSI children are at significantly higher risk for both MenW and Men B disease and should be considered for targeted programs to reflect disease risk
- Meningococcal B disease remains a public health concern with young infants most at risk and UK data demonstrates short-term effectiveness
- Adolescent meningococcal B vaccines likely to provide direct protection against most MenB disease but impact on carriage will be critical to cost effectiveness

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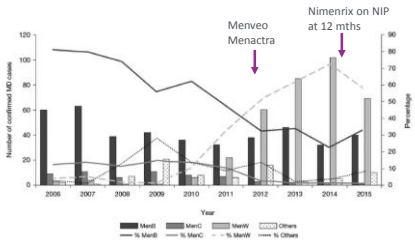
Questions?

MenACWY Vaccine introduction into Chile for young children 9 mths to 5 yrs of age



Borrow Exp Rev Vaccines 2016

ATAGI MenACWY recommendations

- Conditions with increase risk of meningococcal disease
  - defects in or deficiency of complement components, including factor H, factor D or properdin deficiency
  - current or future treatment with eculizumab (anti C5 complement)
  - functional or anatomical asplenia
  - HIV infection, regardless of stage of disease or CD4+ count
  - haematopoietic stem cell transplant
  - These patients require at least 2 doses 8 weeks apart (infants 3+1 doses) with regular 5 yearly boosters
- Travellers to high risk areas
- Laboratory personnel working with meningococci
- Any person aged ≥ 2 months or parent/carer wishing to reduce the likelihood of serogroup A, C, W or Y meningococcal disease: particularly children < 5 years & adolescents 15- 19 years

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Vaccine Effectiveness

Doses	Cases vaccinated / total	Average matched coverage	VE (95 %CI)
2+0	9/13 (69%)	92.9%	82.9% (24.1% to 95.2%)
1+0	20/28 (71%)	76.2%	**22.0% (-105% to 67.1%)**

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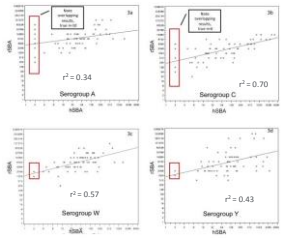
Evaluation of meningococcal ACWY Vaccines: understanding differences in serum bactericidal assays (SBA)

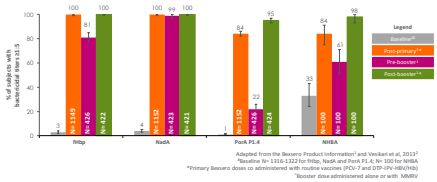
- Complement (C') is critical in antibody mediated killing however meningococci bind inhibitory factor H in serum to decrease this effect
- SBA using human C' (hSBA) initially used but were hard to standardise
- Baby rabbit C' is used however the rabbit FH doesn't bind to test strains so rSBA titres higher than hSBA
- Different companies used rSBA or hSBA as primary immunogenicity assay for evaluating MenACWY conjugate vaccines
- Cannot directly compare results from different studies and different laboratories
- It is likely that hSBA ≥1:4 or rSBA ≥ 1:8 will prove to correlate with vaccine effectiveness for additional W and Y serogroups

McIntosh Vaccine 2015 33:4415-21



Correlation of SBA titres in adolescents 1 month post-MenACWY-CRM vaccine *Gill Vaccine 2011*

Infant response to vaccination with Bexsero[1,2]



Adapted from the Bexsero Product Information[1] and Vesikari et al, 2013[2]
[a]Baseline N= 1316-1322 for fHbp, NadA and Pork P1.4; N= 100 for NHBA
[1]Primary Bexsero doses co administered with routine vaccines (PCV-7 and DTP-IPV-HBV/Hib)
[2]Booster dose administered alone or with MMRV

Vaccinated at time points compatible with the NIP (2,4,6 and 12 months), measured one month following vaccination

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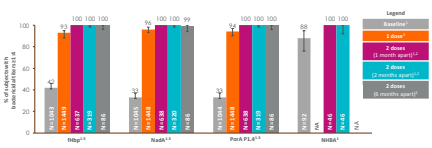
Adolescent response to vaccination with Bexsero



Adapted from the Bexsero SmPC[1], the Bexsero Product Information[2] and Santolaya et al, 2012[3]

Baseline: For fHbp, NadA and Pork P1.4 data from 0-1, 0-2 and 0-6 month groups; for NHBA data from 0-1 and 0-2 month groups. Data shown are 1 month post the last dose in the series. A high proportion of subjects had high pre-existing hSBA titers against the meningococcal test strains at baseline, which may be due to nasopharyngeal carriage, suggesting environmental exposure. NA = Not Assessed

Flexible dosing schedules (2 doses given at 1, 2 or 6 months apart; aged 11-17 years)

1. Bexsero Summary of Product Characteristics, European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/002333/WC500139983.pdf (accessed March 2016) 2. Bexsero Product Information 3. Santolaya et al. Lancet 2012; 379:617-24