Invasive Meningococcal Disease (IMD)
An update on prevention in Australia

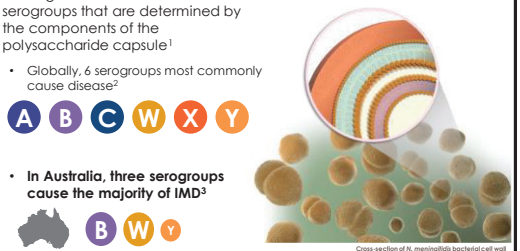
Invasive Meningococcal Disease

Caused by the bacterium *Neisseria meningitidis*[1]

- Meningococci are classified into serogroups that are determined by the components of the polysaccharide capsule[1]
  - Globally, 6 serogroups most commonly cause disease[2]

A B C W X Y

- **In Australia, three serogroups cause the majority of IMD[3]**



B W Y

Cross-section of *N. meningitidis* bacterial cell wall
(adapted from Rosenstein et al)[4]

1. Australian Technical Advisory Group on Immunisation (ATAGI). *The Australian Immunisation Handbook* 10th Edition (2018 update) . Canberra: Australian Government Department of Health, 2018 [Accessed September 2018]
2. Meningococcal meningitis factsheet No 141. World Health Organization website. http://www.who.int/mediacentre/factsheets/fs141/en/ [Accessed February 2017]
3. Lahra and Enriquez. *Commun Dis Intell* 2016; **40 (4)**:E503-E511
4. Rosenstein NE, et al. *N Engl J Med*. 2001; **344**:1378-1388

Symptoms are difficult to diagnose at early onset and develop rapidly[1,2]

Medical intervention often does not occur until late

13-24 HOURS
POTENTIALLY LETHAL
Most progressed from non-specific initial symptoms to close to death within 24 hours

~ 13 hours - Median time to first hospitalisation*

- **Neck pain and stiffness**
- **Hemorrhagic rash**
- Floppy muscle tone#
- **Bulging fontanelle***
- Photophobia
- Confusion and delirium^
- Seizure

*In infants <1 year
#In children < 5 years
^In children > 1 year

24 HOURS

8 – 12 HOURS

~8 hrs – Median time to first GP consultation*

- **Cold hands and feet**
- **Abnormal skin colour**
- **Breathing difficulty**
- **Increased thirst**
- **Diarrhoea**

*In infants <1 year

0-7 HOURS
NON SPECIFIC SYMPTOMS

- **Fever**
- **Irritability**
- Nausea or vomiting
- Poor appetite or feeding
- Drowsiness
- Headache^
- Sore throat
- Thirst
- Leg pain
- General aches

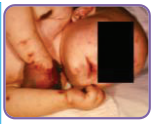
^In children > 1 year

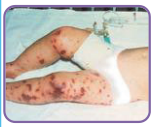
1. Thompson MJ, et al. *Lancet* 2006; **367**:397–403
2. van Deuren M, et al. *Clin Microbiol Rev* 2000; **13**:144–166

Meningococcal disease can be deadly and devastating[1-3]

- Significant morbidity and mortality despite early diagnosis and appropriate medical treatment
  - **~10% of cases** are fatal[1,2]

  - Up to **1 in 5 survivors** of IMD (all serogroups) have **permanent sequelae**[1,2]
  - Child survivors may experience major sequelae eg limb **amputations, seizures and hearing loss**[3]
    - ~30% experience other deficits such as psychological disorders, digit amputations and unilateral hearing loss[3]

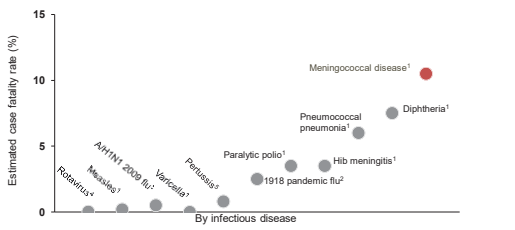




Top image: Courtesy of Centres for Disease Control and Prevention and Dr. Gust. Bottom image: Courtesy of Meningitis Research Foundation UK. Available at www.meningitis.org

1. Meningococcal meningitis factsheet No 141. World Health Organization website. http://www.who.int/mediacentre/factsheets/fs141/en/
2. Rosenstein NE, et al. *N Engl J Med*. 2001; **344**:1378-1388
3. Viner RM, et al. *Lancet Neurol*. 2012; **11**:774-783.

IMD associated with a higher case fatality rate compared with other VPDs



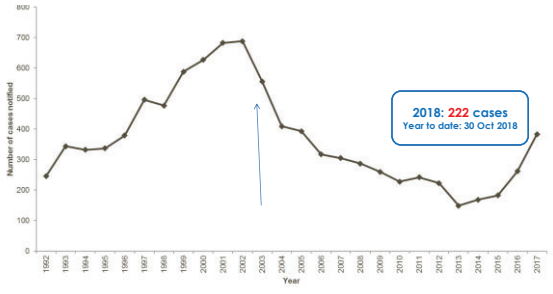
Notes: Meningococcal disease and Hib meningitis: despite appropriate antimicrobial therapy; paralytic polio: in children; 1918 pandemic flu: in young adults; varicella: in children and adolescents; A/H1N1 2009 flu: worldwide; measles: US, 1985–1992; rotavirus: US general population; pertussis: infants <6 months of age, US, 2001–2003.

1. Centers for Disease Control and Prevention (CDC). *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. Atkinson W, et al., eds. Washington, DC: Public Health Foundation; 2012. http://www.cdc.gov/vaccines/pubs/pinkbook/index.html#chapters; 2. Taubenberger JK, et al. *Emerg Infect Dis*. 2006;12:15-22; 3. Pandemic H1N1 2009 Overview. CIDRAP website. http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/biofacts/h1n1_panview.html; 4. Gerba CP, et al. *Wat Res*. 1996;30:2929-2940; 5. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep*. 2005;54:1283-1286.

IMD = invasive meningococcal disease VPDs = vaccine preventable diseases

Notifications of invasive meningococcal disease

Australia, 1992- 2017, by year, all serogroups ***2013-2017: 4 yrs***[1]

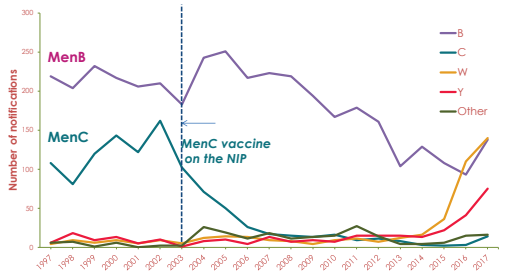


Adapted from National Notifiable Diseases Surveillance System[1]

1. National Notifiable Disease Surveillance System (NNDSS). http://www9.health.gov.au/cda/source/rpt_3.cfm [Accessed October 2018]

Introduction of MenC vaccine to NIP

Australia, 1997- 2017, by year and bacterial serogroup



Adapted from the Annual reports of the meningococcal surveillance program[1] and the Department of Health, 2017[2]
Note: "Other" includes other serogroups not singled out, cases where meningococcal isolates could not be identified, other isolates not grouped and cases where serogroup was not known.

1. Annual reports of the Australian Meningococcal Surveillance programme, 1997-2016 http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-pubs-annlrpt-mensanrep.htm (Accessed January 2018)
2. Department of Health. Invasive Meningococcal Disease National Surveillance Report: with a focus on MenW. 31 December 2017. http://www.health.gov.au/internet/main/publishing.nsf/Content/SFEABC48495BDEC1CA25807D001327FA/$File/31-Dec17-IMD-Surveillance-report.pdf (Accessed February 2018)

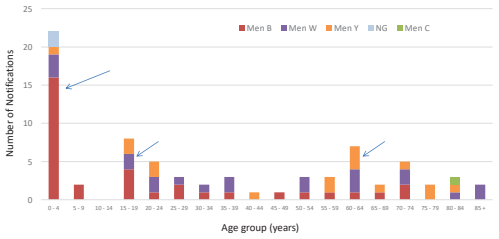
IMD Australia: Breakdown by State or Territory, 2018[1]

Most cases in NSW, QLD, Vic

1. Adapted from the National Notifiable Diseases Database Surveillance System and Australian Government (accessed 10 Feb 2019).

Meningococcal disease by age, NSW, 2018

Breakdown by age bands

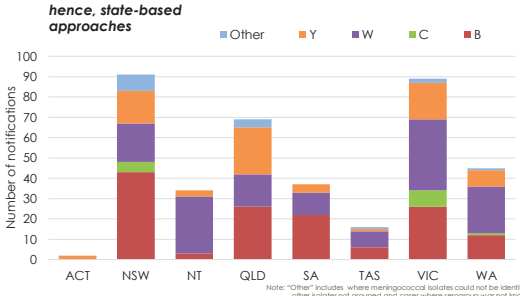


NSW Health - [Accessed Feb 2019]
https://www1.health.nsw.gov.au

IMD Australia: Breakdown by State or Territory, 2017

Peak disease: B in SA, NSW, QLD W in Vic, WA, NT

hence, state-based approaches



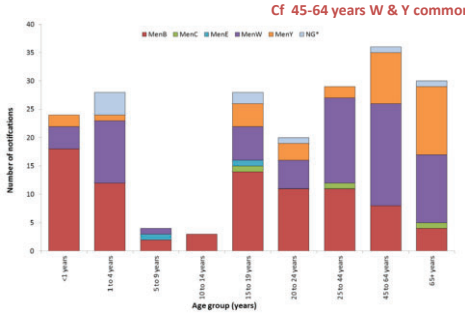
Note: "Other" includes where meningococcal isolates could not be identified, other isolates not grouped and cases where serogroup was not known.

Adapted from Department of Health. Invasive Meningococcal Disease National Surveillance Report: with a focus on MenW. 31 December 2017. http://www.health.gov.au/internet/main/publishing.nsf/Content/SFEABC48495BDEC1CA25807D001327FA/$File/31-Dec17-IMD-Surveillance-report.pdf [Accessed February 2018]

Australia-wide, 1 January to 30 September 2018#

Breakdown by age

Nb <1 year & 15-24 years B = #1
Cf 45-64 years W & Y common

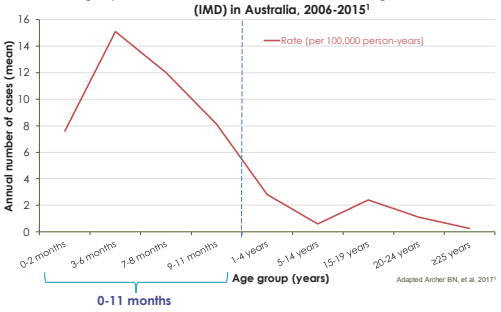


*Data were extracted from the NNDSS on 1 August 2018, by diagnosis date.
*NG includes where meningococcal isolates could not be identified ('not groupable'), other isolates not grouped and where serogroup was not known.

Invasive Meningococcal Disease National Surveillance Report – 1 April to 30 September 2018 - [Accessed Jan 2019] http://www.health.gov.au/internet/main/publishing.nsf/Content/5FEABC48495BDEC1CA25807D001327FA/$File/QTR-2-IMD-Surveillance-report-30Jun18.pdf

2006 to 2015 data shows that notification rates for meningococcal B hit 2 peaks: <5 years and aged 15-19 years

Age-specific numbers and rates of invasive meningococcal disease (IMD) in Australia, 2006-2015[1]

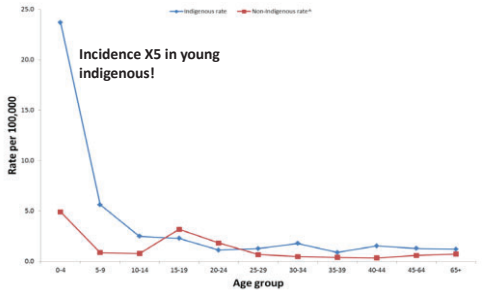


Adapted Archer BN, et al. 2017[1]

1. Archer BN, et al. MJA. 2017; 207(9):382-387

IMD notification rates, Australia

By Indigenous status and age group, 2002-2018 YTD#

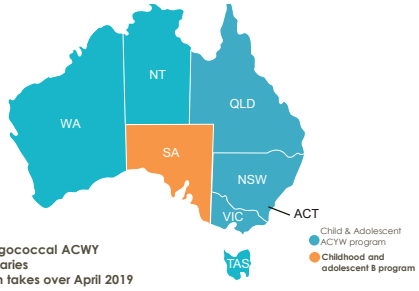


#Data from the NNDSS with a diagnosis date up until of 31 March 2018. Data was extracted on 23 April 2018.
^Non-Indigenous includes case reported as non-Indigenous and not stated.

1. Australian Government Department of Health. Invasive Meningococcal Disease National Surveillance Report with a focus on MenW 31 March 2018.

National/State-based *MenACWY vaccination programs*[1]

Target adolescents, due to highest carriage rate and hi disease rate



Brand of meningococcal ACWY vaccine used varies Commonwealth takes over April 2019

1. Relevant State health departments. References provided at end of slide deck.
States and Territories may also implement additional programs or on an as-needed basis

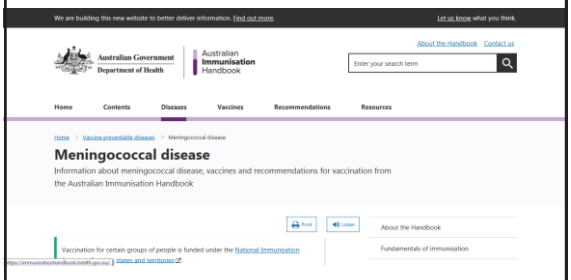
NIP childhood schedule From 1 July 2018

Changes then and now

Age	Disease
Birth	Hepatitis B[a]
2 months (from 6 weeks of age)	DTPa-IPV-HBV/Hib PCV13 Rotavirus[b]
4 months	DTPa-IPV-HBV/Hib PCV13 Rotavirus[b]
6 months	DTPa-IPV-HBV/Hib
12 months	**MenACWY** MMR PCV13
18 months	Hib MMRV DTPa
4 years	DTPa-IPV

a Hepatitis B vaccine: Should be given to all infants as soon as practicable after birth. The greatest benefit is if given within 24 hours, and must be given within 7 days.
b Rotavirus vaccine: First dose must be given by 14 weeks of age, the second dose by 24 weeks of age.

Australian Immunisation Handbook (AIH): Meningococcal vaccination recommendations



***Refer also to NCIRS meningococcal fact sheet & FAQs**

Recommendations

All infants, children and adults

Any person from 6 weeks of age who wants to protect themselves against meningococcal disease is recommended to receive MenACWY vaccine and MenB vaccine

Infants and children

Infants and children aged <2 years are strongly recommended to receive MenACWY vaccine

Infants and children aged <2 years are strongly recommended to receive MenB vaccine

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Adolescents

Healthy adolescents aged 15–19 years are strongly recommended to receive MenACWY vaccine

Healthy adolescents aged 15–19 years are strongly recommended to receive 2 doses of MenB vaccine

Aboriginal and Torres Strait Islander people

Aboriginal and Torres Strait Islander people aged 2 months to 19 years are strongly recommended to receive MenACWY vaccine

All Aboriginal and Torres Strait Islander people aged 2 months to 19 years are strongly recommended to receive MenB vaccine

19

People with medical conditions that increase their risk of invasive meningococcal disease

People with medical conditions that increase their risk of invasive meningococcal disease are strongly recommended to receive MenACWY and MenB vaccines

Laboratory workers

Laboratory workers who frequently handle Neisseria meningitidis are strongly recommended to receive MenACWY and MenB vaccines

Travellers

People who travel to areas where meningococcal disease is more common, or who travel to mass gatherings such as the Hajj, are strongly recommended to receive MenACWY vaccines

Young adults living in close quarters

Adolescents and young adults living in close quarters are strongly recommended to receive MenACWY and MenB vaccines

Smokers

Adolescents and young adults who are current smokers are strongly recommended to receive MenACWY and MenB vaccines

Meningococcal vaccines

The National Immunisation Program (NIP), state programs & private vaccines

Meningococcal C
Introduced to the **NIP** in 2003
Drastic reduction in disease

Meningococcal A,C, W & Y
Introduced to the **NIP** July 2018 to replace MenC +Hib at 12 months (Hib at 18 ths)
All **states & territories** except SA have/had **adolescent** programs*
From **April 2019**, MenACWY vaccination of **adolescents** to be introduced to the **NIP**
Private prescription ≥ 6 weeks of age

Meningococcal B
Not currently on the **NIP**
Oct 2018, **SA program** for those aged 0-4 years
2019 program for 15-20 year olds
Private prescription in all other states for ≥ 2 months of age

1. Australian Technical Advisory Group on Immunisation (ATAGI). *The Australian Immunisation Handbook* 10th Edition (2017 update) . Canberra: Australian Government Department of Health, 2017

*The specifics of each program varies, including the brand of vaccine used. Please refer to your state or territory health department for more details. Note: some programs may have now ended.

Quadrivalent ACWY meningococcal vaccines[1]

Meningococcal A, C, W and Y conjugate vaccines

Vaccine	Indication	Dosing schedule
Menveo[2] GSK	≥2 months	<6 months, 4 doses 7-23 months, 2 doses ≥2 years, 1 dose
Nimenrix®[3] *Pfizer*	**≥6 weeks**	**6-12 weeks, 3 doses** **≥12 months, 1 dose**
Menactra®[4] *Sanofi-Aventis*	≥9 months–55 years	9-23 months, 2 doses 2-55 years, 1 dose

Generally well tolerated, with the most common side effects (>10%) typically associated with vaccination

- ie. Injection site reactions, gastrointestinal upset, headache, fatigue. Not a complete list, refer to PI's for full details[2-4]

1. Australian Technical Advisory Group on Immunisation (ATAGI). *The Australian Immunisation Handbook* 10th Edition (2016 update) . Canberra: Australian Government Department of Health, 2016 [Accessed February 2017]
2. Menveo Product Information, GSK
3. Nimenrix Product Information, Pfizer
4. Menactra Product Information, Sanofi-Aventis

Meningococcal B vaccines[1-2]

Recombinant meningococcal B vaccines

Vaccine	Indication	Antigen/s	Dosing schedule
Bexsero[1] **GSK**	**≥2 months**	• fHbp* • NadA^ • NHBA# • NZ PorA P1.4: porin A	Variable, depending on age at first administration
Trumenba®[2] *Pfizer*	≥10 years	• fHbp* subfamily A (A05) • fHbp *subfamily B (B01)	Variable, depending on patient risk of IMD

*Factor H Binding Protein
^Neisseria Adhesin A protein (rbe)
#Neisseria Heparin Binding Antigen fusion protein (rbe)

Bexsero and Trumenba are recombinant, **inactive** vaccines (ie. not live vaccines)

1. Bexsero Product Information GSK
2. Trumenba Product Information, Pfizer

Men B vaccine PI update:

Approved dosing schedules for Bexsero in Australia

Administer by **deep intramuscular injection**, preferably in the anterolateral aspect of thigh in infants or deltoid muscle region of upper arm in older subjects

Dosage:	*Primary immunisation*	*Minimum interval between primary doses*	*Booster*
Infants 2-5 months*	**2 doses** 3 doses	**≥ 2 months** ≥ 1 month	**Second year of life** (≥6 months post primary series)
Infants 6-11 months	2 doses	≥ 2 months	Second year of life (≥2 months post primary series)
Toddlers 12 months - 23 months	2 doses	≥ 2 months	Need not established
Children (≥2 years), **Adolescents & Adults**^	**2 doses**	**≥ 1 month**	

*The safety and efficacy of the vaccine in infants <8 weeks have not been established. No data available
^The safety and efficacy of the vaccine in individuals above 50 years of age have not been established

1. Bexsero Product Information

Bexsero update: Real world experience

UK
Introduction of national vaccination campaign (2+1 schedule)

10 months after program introduction → 50% reduction in MenB cases in vaccine-eligible infants[3]

Canada
Regional vaccination campaign in Saguenay–Lac-Saint-Jean, Quebec and vaccination during a MenB outbreak at Acadia University, Nova Scotia

USA
Vaccination during MenB outbreaks at Princeton University, University of California at Santa Barbara, and Santa Clara University

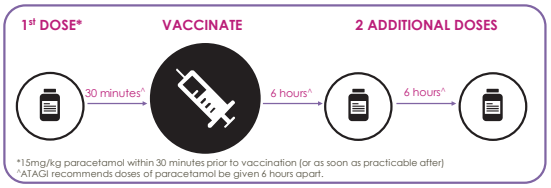
Infants >2mths

Adolescents

1. Watson P and Turner D. Vaccine 2016;**34**:875–880
2. Ladhani et al. *Arch Dis Child* 2016;**101**:91–95
3. Bexsero PI

Recommendations: Bexsero and Prophylactic Paracetamol, age < 2 years

Australian Technical Advisory Group on Immunisation (ATAGI)[1]



*15mg/kg paracetamol within 30 minutes prior to vaccination (or as soon as practicable after)
^ATAGI recommends doses of paracetamol be given 6 hours apart.

- Prophylactic use of paracetamol reduces the incidence and severity of fever without affecting the immunogenicity of either Bexsero or routine vaccines (PCV-7 and DTP-IPV-HBV/Hib)[2]
- The effect of antipyretics other than paracetamol on the immune response has not been studied[2]

1. Australian Technical Advisory Group on Immunisation (ATAGI). *The Australian Immunisation Handbook* 10th Edition (2016 update) . Canberra: Department of Health.
2. Bexsero Product Information

Summary

- **IMD is a rare, but potentially fatal disease**
  - **difficult to diagnose** early due to non-specific symptoms
  - **symptoms develop rapidly**
  - even with appropriate medical treatment up to 10% of cases are fatal and up to 30% of survivors suffer from permanent sequelae
- **Changing epidemiology** has influenced changes to funded programs
  - **MenACWY vaccine provided under NIP at 12 mth encounter: July 2018 (replaced MenC + Hib)**
  - **From April 2019, MenACWY vaccine will be available on the NIP for 14-16 year old's (catch-up program for those aged 15-19 years)**
- In **2018 & many other years**, **MenB** was the **predominant** serogroup in Australia
  - ***1 Oct 2018, SA introduced a State-based funded MenB program for infants and (from 1 Feb 2019) adolescents***
  - In all other states MenB is available on private prescription
- **ATAGI strongly recommend MenB and MenACWY vaccination for at-risk groups**
- **Bexsero PI update includes a 2+1 vaccination schedule for those aged 2-5 months**

Vaccine recommendations

Any person aged 6+ weeks ***who wishes to protect themselves*** against meningococcal to have **both MenACWY & MenB vaccines**

These vaccines are **strongly recommended for** :

Infants aged 6 weeks < 2 years
Teens aged 15 - 19 years
All indigenous aged 2 months – 19 years
High risk conditions e.g. lab, crowded, smokers (15-24 years)
Travellers e.g. "meningitis belt", Hajj

All are considered high risk

Menactra, Menveo, Nimenrix (ACWY)

- Age <2 years: no preference; Menveo & Nimenrix 2/12 start, Menactra start from 9/12 of age
- If 12-23/12 one dose Nimenrix, two doses of other 2; best not give a Tet Tox vaccine 1/12 before Nimenrix (carrier interference)
- Age 2+ years: single dose of any,
  Menactra less favoured – less antibody and declines more
- Menactra not given with PCV13 as less pneumo antibody, but can give PCV13 first then 1/12 gap to Menactra
- Menactra must be given with or one month before Dip Tox, to prevent carrier interference

Bexsero and Trumenba

- Bexsero = recombinant, multi-component, given from 6 weeks
- Trumenba = recombinant, bivalent, from 10 years
- No preference for either if age 10+ years
- Should not mix schedules – if aged 10+ give 2 doses of each
- *(Mixing is OK with MenACWY vaccines)*

MenACWY and MenB vaccines are equally important from a clinical/public health perspective, but as yet only MenACWY is on the National Immunisation Program

Bexsero dosing schedule changes

2+1 schedule in infants:
change to update dosing schedule for infants 2 through 5 months of age to allow for a 2+1 dose schedule

0, 1 month schedule in children:
change to support a 0, 1 month schedule in unvaccinated children 2 through 10 years of age. Currently it is a 0, 2 month schedule.

Age at first dose	Primary Immunisation	Intervals between Primary Doses	Booster
Infants, 2 months to 5 months*	Two doses each of 0.5 ml	Not less than 2 months	Yes, 1 dose in the second year of life, from the age of 12 months or later, with an interval of at least 6 months between the primary series and booster dose
	Three doses each of 0.5 ml	Not less than 1 month	
Infants, 6 months to 11 months	Two doses each of 0.5 mL	Not less than 2 months	Yes, 1 dose in the second year of life with an interval of at least 2 months between the primary series and booster dose
Toddlers, 12 months to 23 months	Two doses each of 0.5 mL	Not less than 2 months	Need not established
Children, 2 years to 10 years	Two doses each of 0.5 mL	Not less than 1 month	Need not established
Adolescents (from 11 years) and adults*	Two doses each of 0.5 mL	Not less than 1 month	Need not established

* The first dose should be given no earlier than 2 months of age. The safety and efficacy of Bexsero in infants less than 8 weeks of age has not yet been established. No data are available.

Australian Immunisation Handbook

Meningococcal recommendations

Age group	Healthy Aboriginal and Torres Strait Islander people	Healthy non-Indigenous people	Special risk groups (including adolescent and young adult smokers and those living in close quarters; and laboratory workers)	Travellers to regions with an increased risk of exposure to MenACWY disease
6 weeks–23 months	MenB and MenACWY[a]	MenB and MenACWY[a]	MenB and MenACWY[a]	MenACWY[a]
2–4 years	MenB and MenACWY	None	MenB and MenACWY	MenACWY
5–14 years	MenB and MenACWY	None	MenB and MenACWY	MenACWY
15–19 years	MenB and MenACWY	MenB and MenACWY	MenB and MenACWY	MenACWY
≥20 years	None	None	MenB and MenACWY	MenACWY

UK PHE MenB vaccination program

- 74% reduction in Men B disease in the vaccinated cohort
- Men B program has prevented ~ 250 cases
- Men ACWY program has prevented ~ 50 cases
- No safety signals identified from 5 million doses administered

UK Safety Experience with Bexsero[1,2]

Sep 2015-May 2017

~1.29 million infants vaccinated*

Analysis of suspected adverse reactions:
- Passive surveillance (Yellow Card Scheme)
- Data analysis from the Clinical Practice Research Datalink (CPRD)

Safety findings

- **902 adverse reaction reports**†
  Most common: local reactions (41%), fever (40%)
- **No new safety signals** identified
- Anticipated reactogenicity did **not affect compliance** with subsequent doses
- To date, UK experience shows 4CMenB has a **favourable benefit–risk profile**

The safety profile of 4CMenB was broadly as expected, with no serious safety concerns identified

- *1.29 million infants aged 2-18 months received a combined 3 million doses between Sep 2015 to May 2017
- † Mainly relating to fever (40% and localised reactions (41%), and equates to 2429 adverse events

Carriage of *N. meningitidis* in high school students

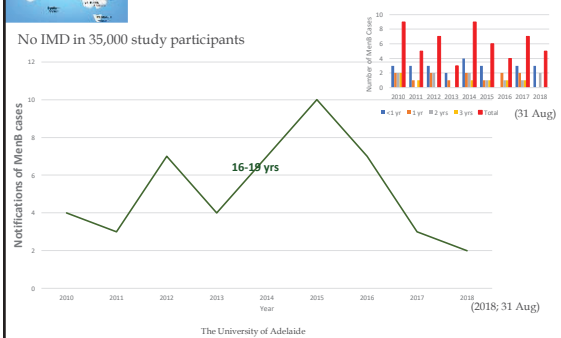
"B Part of It" study

- Professor Helen Marshall
- NHMRC Senior Research Fellow
- Senior Medical Practitioner and Director VIRTU, Women's and Children's Health Network
- Deputy Director, Robinson Research Institute, University of Adelaide

Preliminary results presented at IPNC, USA Sep 2018

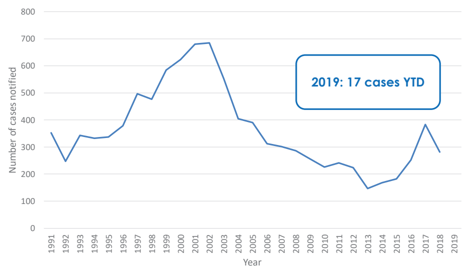
IMD serogroup B notifications in adolescents in SA pre and post study implementation

No IMD in 35,000 study participants



Notifications of invasive meningococcal disease

Australia, 1991- 2017, by year, all cases of IMD



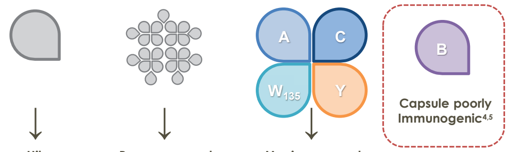
Adapted from National Notifiable Diseases Surveillance System[1]

1. National Notifiable Disease Surveillance System (NNDSS). http://www9.health.gov.au/cda/source/rpt_3.cfm [Accessed 11 Dec 2018]

IMD vaccine development

Conventional approaches have not been possible for MenB

H influenzae[1] (1 pathogenic serotype)	*S pneumoniae*[2] (23 pathogenic serotypes^)	*N meningitidis*[3] (5 pathogenic serogroups)
INVASIVE DISEASE	INVASIVE DISEASE	INVASIVE DISEASE



Hib Glycoconjugate vaccine	Pneumococcal Glycoconjugate vaccine	Meningococcal Glycoconjugate vaccine

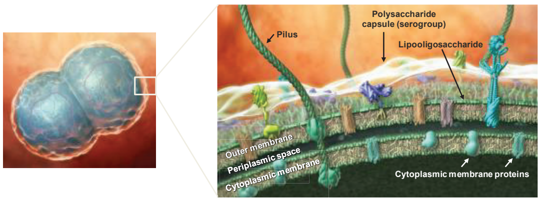
^23 pathogenic serotypes, causing 90% of invasive disease in developed countries

1. Watt JP, et al. *J Pediatr* 2003; **143**:S163–S187
2. WHO fact sheet. Pneumococcal disease 2013. http://www.who.int/biologicals/vaccines/pneumococcal/en/ [Accessed January 2017]
3. Girard MP, *et al. Vaccine* 2006; **24:**4692–4700
4. Finne J, *et al. J Immunol* 1987;**138**:4402–4407
5. Wyle FA, et al. *J Infect Dis*. 1972;**126**:514–521

Bexsero contains 4 antigenic components (4CMenB vaccine)

Identified using a "reverse vaccinology" approach

Bexsero = 3 recombinant surface-exposed protein antigens + OMV[1]



NHBA: Neisseria Heparin-Binding Antigen + GNA fusion protein

fHBP: factor H Binding Protein + GNA fusion protein

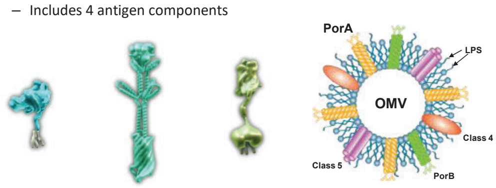
OMV: NZ PorA P1.4: porin A

NadA: Neisseria adhesin A Protein

- Images are © Hurd Studios, 2012 and courtesy of GlaxoSmithKline
- 1. Madico G *et al. J Immunol* 2006;177:501–510

Bexsero Consists of 3 Protein Antigens and an Outer Membrane Vesicle (OMV)*

- Multicomponent (4) Meningococcal Serogroup B Vaccine
  - Has the potential to protect against the majority of MenB disease
  - Includes 4 antigen components



fHbp* **NadA** **NHBA*** **PorA 1.4 (as part of OMV†)**

*Fusion proteins; fHbp-GNA2091 and NHBA-GNA1030.
†OMV from a hyperendemic New Zealand *Neisseria meningitidis* serogroup B strain measured as amount of total protein containing the PorA P1.4.
fHbp=factor H–binding protein; NadA=Neisserial adhesin protein A; NHBA=Neisseria heparin–binding protein; PorA=porin A.

Bexsero approvals and recommendations

More than 20 million doses distributed worldwide since launch

41 APPROVALS
- EU/EEA: 31 countries (plus Andorra)[1]*
- Other: Argentina[2], Australia[3], Brazil[4], Canada[5], Chile[6], Uruguay[7], USA[8]

19 CLINICAL RECOMMENDATIONS†
- Australia[9], Austria[10], Belgium[11], Brazil[12], Canada[13], Cyprus[14], Czech Republic[15], France[16], Germany[17], Greece[18], Hungary[19], Poland[20], Portugal[21], Spain[22]
- Andorra[23], Ireland[24], Italy[25], UK[26], USA[27] (see below)

9 NIPs
- Andorra[23], Ireland[24], Italy[25], Lithuania, Malta, Portugal, UK[26]: NIPs implemented
- USA: Category B national recommendation[27]

NIPs, National Immunisation Programmes
*Bexsero approved across EU and EEA countries under a centralised procedure (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK; Andorra is not listed in EU SmPC, but follows the same approvals as Spain)
†Clinical recommendation in countries where *Bexsero* has been approved

Please refer to slide notes for references