Title: **Clinical outcomes, costs, knowledge and awareness of invasive meningococcal disease in South Australia**

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ABSTRACT

Introduction: Despite appropriate antibiotic therapy, invasive meningococcal disease (IMD) still remains a leading infectious cause of death in childhood in developed countries. We aimed to

1. describe the clinical burden of sequelae following IMD and identify predictors of sequelae in South Australian children;

2. estimate and compare the inpatient costs and hospital service use associated with IMD by serogroup, age, sequelae, gender, previous medical diagnosis and clinical type in South Australian children;

3. assess community, parent and adolescent knowledge and awareness of IMD in South Australia.

Methods:

1. Clinical details were collected from medical records of children admitted to a tertiary paediatric hospital in South Australia with a diagnosis of IMD from 2000 to 2011. Logistic regression was used to identify predictors of sequelae.

2. Inpatient costs were provided by the Health Informatics, Performance, Planning and Outcomes Unit at the Women's and Children's Hospital (WCH) in South Australia and inflated to 2011 Australian dollars using the medical and hospital services component of the Australian Consumer Price Index.

Multivariate regression was used to determine predictors of higher inpatient costs, longer hospital stay and increased hospital service use.

3. A cross-sectional survey was conducted through face to face interviews, with 5200 households randomly selected in metropolitan and rural South Australia in 2012. 3055 interviews were conducted with questions regarding IMD knowledge and concern asked in the survey. The survey was developed by the staff members of Vaccinology and Immunology Research Trials Unit (VIRTU) at the WCH. Logistic regression analyses were performed with the survey data weighted to reflect 2011 Census figures.

Results:

1. Of 109 children hospitalised with IMD, 54.1% were female and 11.9% Aboriginal. The majority of cases were caused by serogroup B (70.6%) with 9.2% caused by serogroup C, 2.7% caused by serogroup Y or W135. The serogroup of the remaining patients (17.4%) was unknown including 12 patients (11.0%) who had the undermined or ungroupable serogroup and 7 patients (6.4%) who were only clinically diagnosed. 37.6% (n=41) had sequelae with 41.3% (31/75) occurring following serogroup B disease and 22.2% (2/9) following serogroup C disease (p=0.280). Sequelae were defined as any complications related to IMD that were not resolved at hospital discharge or occurred after discharge. Children who developed sequelae, were followed up for 5 – 659 days (mean [95% CI]: 645.8 [403.3 to 939.3]) from the acute admission day to the discharge day of the acute hospitalisation if they were not followed up at the WCH OR to the day of

their last IMD related outpatient visit. For children aged less than one year (n=31), sequelae occurred in 100% (4/4) of children with a history of prematurity compared to 44.4% (12/27) of full term infants (p=0.038). Fever ≥ 39°C on presentation to the hospital (OR [95% CI]: 4.5 [1.4 to 14.3]; p=0.012), a diagnosis of septicaemia with meningitis compared to septicaemia alone (OR [95% CI]: 15.5 [4.4 to 54.4]; p<0.001) and meningitis alone (OR [95% CI]: 7.8 [2.2 to 28.3]; p=0.002), and antibiotics given prior to admission (OR [95% CI]: 12.0 [2.0 to 71.6]; p=0.007), are independent predictors of developing sequelae following IMD.

2. Presence of sequelae, serogroup B infection, male gender, infants less than one year of age, and previous medical diagnosis were associated with higher inpatient costs and length of stay (LOS) in hospital (p<0.001) during the acute admission. Serogroup B cases incurred a significantly higher risk of IMD related readmissions (IRR [95% CI]: 21.1 [2.2 to 199.6], p=0.008). During the IMD related readmissions, children with serogroup B infection, male gender, diagnosis of septicaemia, infants less than one year of age, and no previous medical diagnosis were more likely to have higher inpatient costs and LOS (p<0.05).

3. Of 3055 participants in the community survey, 64.9% correctly answered at least two of three questions regarding severity, incidence and susceptibility of IMD and 33.7% expressed high concern about IMD. Age, country of birth, marital status, educational level, household income, residential area and socioeconomic status were associated with levels of IMD knowledge

($p<0.05$). Female gender, married/De Facto, low educational attainment, low household income, parents living in the rural area and low socioeconomic status were predicators of higher concern about IMD ($p<0.05$).

Conclusion: Although IMD is uncommon, the severe outcomes and long-term sequelae are associated with high health care costs. We observed a gap in knowledge about IMD in the community, especially in adolescents that could negatively affect uptake of a new meningococcal vaccine. Our findings could help policy makers globally develop community tailored educational programs in order to improve community awareness of IMD.

THESIS DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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STATEMENT OF CONTRIBUTIONS TO PUBLICATIONS

This thesis contains three manuscripts, which have been submitted to or accepted by international peer-reviewed journals (The Pediatric Infectious Disease Journal (Impact Factor: 3.569), (Vaccine (Impact Factor: 3.492)).

1. Wang B, Clarke M, Thomas N, Howell S, Haji Ali Afzali H, Marshall H. The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children (in press). *Pediatr Infect Dis J*. DOI: 10.1097/INF.0000000000000043
2. Wang B, Haji Ali Afzali H, Marshall H. The economic burden of invasive meningococcal disease in Australian children (under review). *Vaccine*.
3. Wang B, Clarke M, Haji Ali Afzali H, Marshall H. Community, parental and adolescent awareness and knowledge of meningococcal disease (accepted). *Vaccine*.

All these manuscripts were authored by Bing Wang (BW), her two supervisors, Helen Marshall (HM) and Hossein Haji Ali Afzali (HH), and/or other colleagues, Michelle Clarke (MC), Natalie Thomas (NH) and Stuart Howell (SH). BW is the first author of all three manuscripts.

For the first manuscript, BW reviewed the hospital notes, collected data with regards to clinical outcomes for all patients with sequelae following invasive meningococcal disease, and prepared the first draft of the manuscript under the direct supervision of HM and HH. HM assisted with study design, and contributed to, reviewed and edited the manuscript. HH contributed to, reviewed and edited the manuscript. MC assisted with study design, and reviewed and edited the

manuscript. NT assisted with study design, reviewed the hospital notes, collected data, and reviewed and edited the manuscript. SH assisted with the more complex statistical analyses, and reviewed and edited the manuscript.

For the manuscript entitled “The economic burden of invasive meningococcal disease in Australian children”, BW performed data analyses and prepared the first draft of the manuscript under the direct supervision of HM and HH. HM assisted with study design, and contributed to, reviewed and edited the manuscript. HH instructed BW in data analyses, and contributed to, reviewed and edited the manuscript.

For the third manuscript regarding community knowledge of and concern about the meningococcal disease, BW performed the data analyses and prepared the first draft of the manuscript under the direct supervision of HM and HH. HM assisted with study design, and contributed to, reviewed and edited the manuscript. HH contributed to, reviewed and edited the manuscript. MC assisted with study design, and reviewed and edited the manuscript.

I confirm that all three manuscripts have been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. I further confirm that the order of authors listed in the manuscript has been approved by all authors.

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was busy studying. I thank my mum for making me believe that I truly could accomplish whatever I put my mind to.

LIST OF ABBREVIATIONS

4vMenCV	Quadrivalent meningococcal conjugate vaccine
4vMenPV	Quadrivalent meningococcal polysaccharide vaccine
ATAGI	Australian Technical Advisory Group on Immunisation
CI	Confidence interval
CSF	Cerebrospinal fluid
DIC	Disseminated Intravascular Coagulation
EU	European Union
GLM	Generalised linear model
HDU	High dependency unit
HibMenCCV	Haemophilus influenzae type b–meningococcal C combination vaccine
ICD	International Classification of Diseases
ICU	Intensive care unit
IMD	Invasive meningococcal disease
IQR	Interquartile range
IRR	Incidence rate ratio
JCVI	Joint Committee on Vaccination and Immunisation
LOS	Length of stay

MenB	Meningococcal B
MenC	Meningococcal C
MenCCV	Meningococcal C conjugate vaccine
MOSAIC	Meningococcal outcome study in adolescents and in children
NNN	National Neisseria Network
NNDSS	National Notifiable Disease Surveillance System
OMP	Outer Membrane or Porin Proteins
OMV	Outer-membrane vesicle
OR	Odds Ratio
PBAC	Pharmaceutical Benefits Advisory Committee
SD	Standard deviation
SEIFA	Socio-Economic Indexes for Areas
UK	United Kingdom
VIRTU	Vaccinology and Immunology Research Trials Unit
WCH	Women's and Children's Hospital

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Invasive meningococcal disease (IMD) is caused by the bacterium *Neisseria meningitidis*. The bacterium has the ability to cause meningitis, septicaemia or a combination of both. People who develop IMD often have non-specific symptoms including sudden onset of fever, a rash of red purple spots or bruises, cold hands, thirst, joint pain, aching muscles, headache, neck stiffness, photophobia, nausea, vomiting, drowsiness and coma. There are 12 known serogroups causing IMD. These serogroups are distinguished by differences in surface polysaccharides of the outer membrane capsule, and are referred to as A, B, C, 29E, H, I, K, L, W135, X, Y and Z. Globally, serogroups A, B, C, W135 and Y are the most common cause of invasive disease.[1, 2] In Australia, almost 85% of serogroup-confirmed cases are caused by serogroup B.[3] The Meningococci can also be further differentiated by differences in their outer membrane proteins and are referred to as serotypes and serosubtypes.[4] Despite available antibiotic therapy the case fatality rate in Australia is approximately 10%.[5] Meningococcal septicaemia can be severe, causing greater mortality than meningococcal meningitis.[6] IMD has been shown to cause permanent sequelae in approximately 10 to 20% of survivors [7] with some studies showing a sequelae rate of up to 57%.[8] In our study, sequelae is defined as any complications that resulted from IMD and were not resolved at hospital discharge or occurred after discharge.[9]

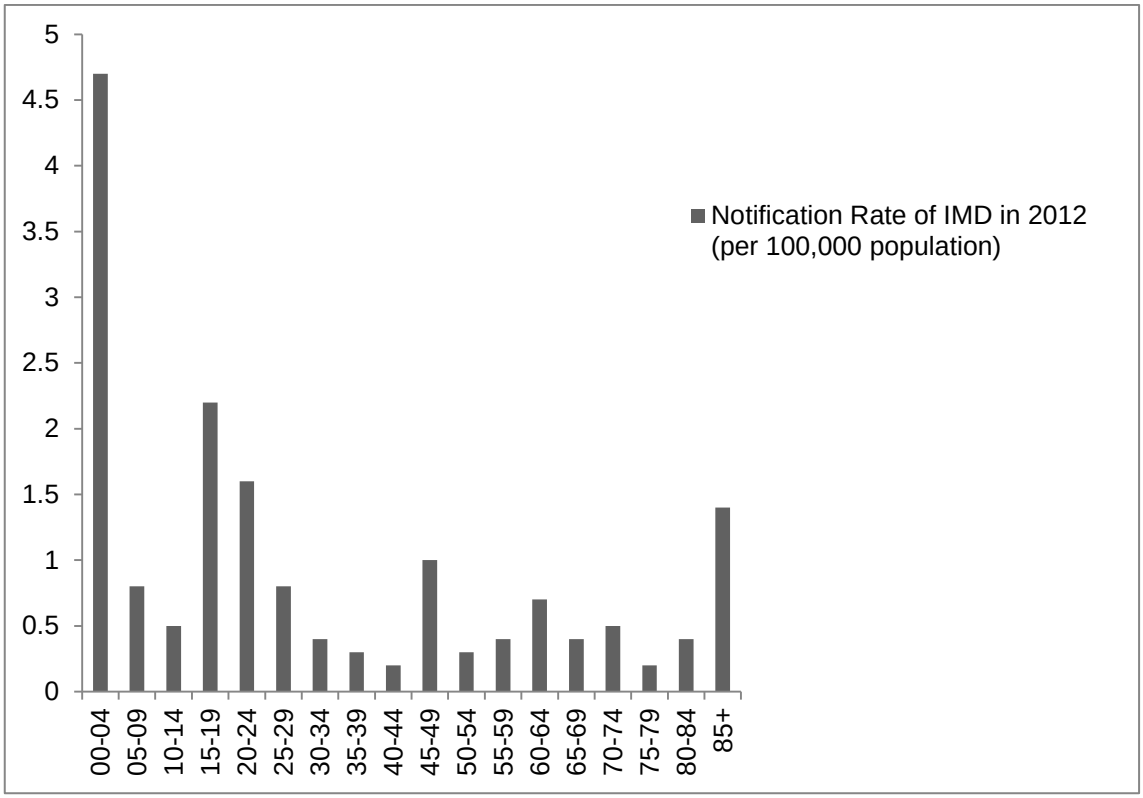
Approximately 200-300 cases of IMD are notified each year in Australia, with the highest number of notifications occurring in New South Wales followed by Queensland, Victoria, Western Australia and South Australia.[3] However, South

Australia had the highest notification rate per 100,000 population (1.8) followed by the Northern Territory (1.7), Queensland (1.4), Tasmania (1.4), New South Wales (0.9), Western Australia (0.7) and Victoria (0.6) with the lowest notification rate (0.3) occurring in the Australian Capital Territory in 2012.[10] The average annual age-specific hospitalisation rate of IMD in Australia between July 2005 to June 2007 was 2.5/100,000 population. The hospitalisation rate in young children aged between 0 and 4 years is higher with an age specific annual average hospitalisation rate of 14.7/100,000.[11] Deaths due to meningococcal infection in 2009 included 6 males and 3 females with a quantified "years of potential life years lost" equal to 215.[12]

Whilst meningococcal disease in Australia affects all age groups, the surveillance data shows a bimodal age distribution with the highest rates in the 0 to 4 year age group and a second peak in the 15 to 24 year age group.[5] Since the implementation of the national meningococcal C vaccination program in 2003, people aged 35 years or over comprise approximately 18% of all notifications. Furthermore, in 2009, 33% of notified IMD cases in Australia were in children less than four years. Similar proportions were reported in 2007 and 2008. During 2012, 26% of cases occurred in people aged 15 to 24 years with 31% of cases occurring in children aged 0 to 4 years (Figure 1).[13]

Figure 1: Notification rate of IMD Australia, 2012 by age group

Adapted from national notification data provided the National Notifiable Diseases Surveillance System



IMD is the most common infectious cause of death in children in developed countries [14] and as such warrants further investigation into clinical outcomes, direct medical costs and community knowledge of this devastating infection. To the best of our knowledge, limited research has been conducted to evaluate clinical outcomes of IMD in Australia, especially in Australian children.[15-18] No research has been conducted to examine the outcomes of IMD in the post meningococcal C vaccine era. Inpatients costs of IMD have not been estimated in Australia. A number of costing studies were conducted in the US and UK. However, the studies have limitations. For example, they either used administration databases without serogroup data and coding verification, or a

small biased sample of severe case scenarios based on literature review, interviews with survivors and discussion with clinicians.[19-24] Online surveys, questionnaire and interview studies were conducted to evaluate parental knowledge of IMD.[25-28] The generalisability of these studies is limited due to selection bias of the study sample. For example, the parents with high socioeconomic status was more likely to complete the online survey,[25] and the response rate was only 24% in another survey study.[26] Adolescents' knowledge of, attitude towards and concern about IMD have not previously been assessed.

In addition, a new MenB vaccine (4CMenB vaccine, Bexsero®) has recently been licensed in Australia and the United Kingdom (UK) following licensing in the European Union (EU).[29] An interim position statement issued from the Joint Committee on Vaccination and Immunisation (JCVI) in the UK has not recommended the new MenB vaccine to be included in routine immunisation programmes due to lack of cost effectiveness.[30] However, further comments from stakeholders and recently published evidence are currently being considered by the JCVI for an update of the interim position report,[31] with more data regarding long-term impact and costs of IMD urgently required. In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) in its meeting in November 2013, has also not recommended the inclusion of the new MenB vaccine on the National Immunisation Program Schedule because of its unfavourable cost-effective estimate.[32] A resubmission is planned to clarify and address issues raised by the PBAC.[33] Data on the clinical outcomes, inpatient costs of IMD in Australian children and community knowledge of IMD, are lacking and warrant urgent review.

To provide information on the impact of the current meningococcal C program on the epidemiology, clinical outcomes, and costs of IMD in Australia, so that policy makers can be appropriately informed of the likely clinical effectiveness and cost-effectiveness of future meningococcal serogroup B vaccination programs and their promotion amongst the Australian community. The following chapters (papers) address this aim by collecting data on sequelae of IMD, predictors of sequelae, costs associated with IMD hospitalisations, and community knowledge of IMD.

1.2 RESEARCH QUESTIONS

Our study aims to investigate clinical outcomes, inpatient costs and hospital service use associated with IMD hospitalisation between April 2000 and April 2011. The goal of this study is also to evaluate community knowledge and awareness of IMD through face to face interviews conducted between September and December 2012.

We addressed the following research questions:

1. What are the associations between sociodemographic/clinical variables and sequelae? (Chapter 3)
2. What are the factors associated with higher inpatient costs and hospital service use for Australian children with IMD? (Chapter 4)
3. Which socio-demographic factors are associated with the level of community knowledge and concern about IMD? (Chapter 5)

A retrospective review can provide data on the outcomes of IMD in South Australian children over a recent but long time period. We have estimated inpatient costs that accrue for the healthcare system due to IMD. Such information is important when deciding on a new public health intervention such as introduction of new vaccines. This requires detailed contemporary data to inform realistic cost effectiveness analyses. Our study results can provide the critical information required to inform this decision. Our study results of community knowledge and awareness of IMD can deliver useful information to guide policy makers and immunisation educators in development of community tailored educational programs in order to effectively improve public awareness and correct

any misconceptions about IMD, which would be required to optimise uptake of a new Men B vaccine.

1.3 THESIS OUTLINE

Chapter 1 provides a brief overview of IMD and relevant research findings. Chapter 2 describes previous studies, identifies research gaps for our research questions and outlines the rationale of the study. Chapter 3 provides results of our first study including predictors of developing sequelae in IMD children admitted to the Women's and Children's Hospital (WCH) during an eleven-year period. A brief report (paper 1) presenting clinical predictors of sequelae following IMD was published in the international peer-reviewed journal "The Pediatric Infectious Disease Journal" (see appendix 1). Chapter 4 (paper 2) describes estimates of inpatient costs, hospital readmissions and outpatients visits related to IMD during the eleven-year period and factors associated with high inpatient costs and hospital service use. Paper 2 has been submitted to the internal peer-reviewed journal "Vaccine" and is currently under review. Chapter 5 describes the results of the analyses of survey data from 3055 interviews with community members to evaluate knowledge and awareness of IMD in the Australian community with paper 3 accepted by the international peer-reviewed Journal "Vaccine" (see appendix 2). Chapter 6 summarises the study findings, the study limitations and further research required, and includes a discussion on the potential implication and translation of the study results.

1.4 REFERENCES

1. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine*. 2009;27 Suppl 2:B51-63.

2. Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, et al. The changing and dynamic epidemiology of meningococcal disease. *Vaccine*. 2012;30 Suppl 2:B26-36.

3. Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2011. *Commun Dis Intell*. 2012 Sep;36(3):E251-62.

4. *Guidelines for the early clinical and public health management of meningococcal disease in Australia* 2007, Communicable Diseases Network Australia, Department of Health and Ageing, Canberra.

5. Jelfs J, Munro R. Epidemiology of meningococcal disease in Australia. *Journal of paediatrics and child health*. 2001;37(5):S3-6.

6. Peltola H. Meningococcal disease: still with us. *Rev Infect Dis*. 1983;5(1):71-91.

7. Granoff DM, Pelton S, Harrison LH. Meningococcal vaccines. *Vaccines*: *Expert Consult-Online*. 2012:388.

8. Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. *Pediatrics*. 2009;123(3):e502-9.

9. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R. The Disease Burden of Invasive Meningococcal Serogroup B Disease in Canada. *Pediatr Infect Dis J*. 2013 Jan;32(1):e20-e25.

10. Notification Rate of Meningococcal disease (invasive)*, received from State and Territory health authorities in the period of 1991 to 2012 and year-to-date

notifications for 2013 [database on the Internet]. Department of Health and Ageing [cited 8 November 2013]. Available from: http://www9.health.gov.au/cda/source/rpt_4.cfm.

11. Chiu C, Dey A, Wang H, Menzies R, Deeks S, Mahajan D, et al. Vaccine preventable diseases in Australia, 2005 to 2007. *Commun Dis Intell*. 2010;34 Suppl:S50-6.

12. Causes of death Australia 2007. Australian Bureau of Statistics; 2009 [Accessed 12 December 2012]; Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3303.02009?OpenDocument.

13. Number of notifications of Meningococcal disease (invasive), Australia, 2012 by age group and sex. Department of Health and Ageing; 2012 [Accessed 23 January 2013]; Available from: http://www9.health.gov.au/cda/Source/Rpt_5.cfm.

14. Hart CA, Thomson AP. Meningococcal disease and its management in children. *BMJ (Clinical research ed*). 2006;333(7570):685-90.

15. Grimwood K, Anderson VA, Bond L, Catroppa C, Hore RL, Keir EH, et al. Adverse outcomes of bacterial meningitis in school-age survivors. *Pediatrics*. 1995;95(5):646-56.

16. Guimont C, Hullick C, Durrheim D, Ryan N, Ferguson J, Massey P. Invasive meningococcal disease--improving management through structured review of cases in the Hunter New England area, Australia. *J Public Health (Oxf)*. 2010;32(1):38-43.

17. Hansman D. Meningococcal disease in South Australia: incidence and serogroup distribution 1971-1980. J Hyg (Lond). 1983;90(1):49-54.

18. Olesch CA, Knight GJ. Invasive meningococcal infection in Western Australia. *J Paediatr Child Health*. 1999;35(1):42-8.

19. Davis KL, Bell TJ, Miller JM, Misurski DA, Bapat B. Hospital costs, length of stay and mortality associated with childhood, adolescent and young adult meningococcal disease in the US. *Appl Health Econ Health Policy*. 2011;9(3):197-207.

20. Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. *Hum Vaccin*. 2011;7(4):458-65.

21. Davis KL, Misurski DA, Miller JM, Bell TJ, Bapat B. Cost of acute hospitalization and post-discharge follow-up care for meningococcal disease in the United States. *Hum Vaccin*. 2011;7(1):96-101.

22. Karve S, Misurski D, Miller J, Davis KL. Costs of Sequelae Associated with Invasive Meningococcal Disease: Findings from a US Managed Care Population. *Health Outcomes Res Med*. 2011;2:e215-e226.

23. O'Brien JA, Caro JJ, Getsios D. Managing meningococcal disease in the United States: Hospital case characteristics and costs by age. *Value Health*. 2006;9(4):236-43.

24. Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease : scenarios of severe meningitis and septicemia. Paediatr Drugs. 2013;15(1):49-58.

25. Bakhache P, Rodrigo C, Davie S, Ahuja A, Sudovar B, Crudup T, et al. Health care providers' and parents' attitudes toward administration of new infant vaccines--a multinational survey. *Eur J Pediatr*. 2013;172(4):485-92.

26. Petousis-Harris H, Turner N, Soe B. Parent views on school based immunisation: A survey of parents of year 1 and 6 in three diverse Auckland schools. *N Z Fam Physician.* 2004;31(4):222-8.

27. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Attitudes and risk perception of parents of different ethnic backgrounds regarding meningococcal C vaccination. *Vaccine*. 2005;23(25):3329-35.

28. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Parents' perceived vulnerability and perceived control in preventing Meningococcal C infection: a large-scale interview study about vaccination. *BMC Public Health*. 2008;8:45.

29. Novartis Media Relations. Novartis vaccine Bexsero® approved in Australia to help protect against MenB disease, a deadly form of bacterial meningitis. [updated 15 August 2013; accessed 07 October 2013]; Available from: http://www.novartis.com/newsroom/media-releases/en/2013/1723151.shtml.

30. Joint Committee on Vaccination and Immunisation (JCVI) interim position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health; 2013 [updated 24 July 2013; accessed 2 September 2013]; Available from: https://www.gov.uk/government/publications/jcvi-interim-position-statement-on-the-use-of-bexsero-meningococcal-b-vaccine-in-the-uk.

31. Update on the outcome of consultation about use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health; 2013 [updated 25 October 2013; accessed 20 November 2013]; Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/252859/JCVI_MenB_Update.pdf.

32. *November 2013 PBAC Outcomes - 1st Time Decisions Not to Recommend*, Pharmaceutical Benefits Advisory Committee (PBAC), The Department of Health, Commenwealth of Australia, viewed 31 Jan 2014, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2013-11>

33. "Patients want "compassion" on meningococcal vaccine", *PharmaDispatch*, viewed 31 Jan 2014, <http://www.pharmadispatch.com/patients-want-compassion-on-meningococcal-vaccine/>

CHAPTER 2: LITERATURE REVIEW

2.1 AETIOLOGY

Neisseria meningitidis (Figure 1), often termed as meningococcus, is a Gram-negative, oxidase-positive and aerobic diplococcic bacterium that can cause IMD.[1] It is believed that Vieusseux was the first person to describe identification of IMD definitively in 1805 in Eaux Vives, a small suburban town of Geneva. He reported 33 patients died of 'spotted fever', with meningitis occurring in the majority of cases, during a period of 3 months.[2] The causative bacterium, *N. meningitidis,* was first isolated by Anton Weichselbaum in Vienna in 1887.[3]

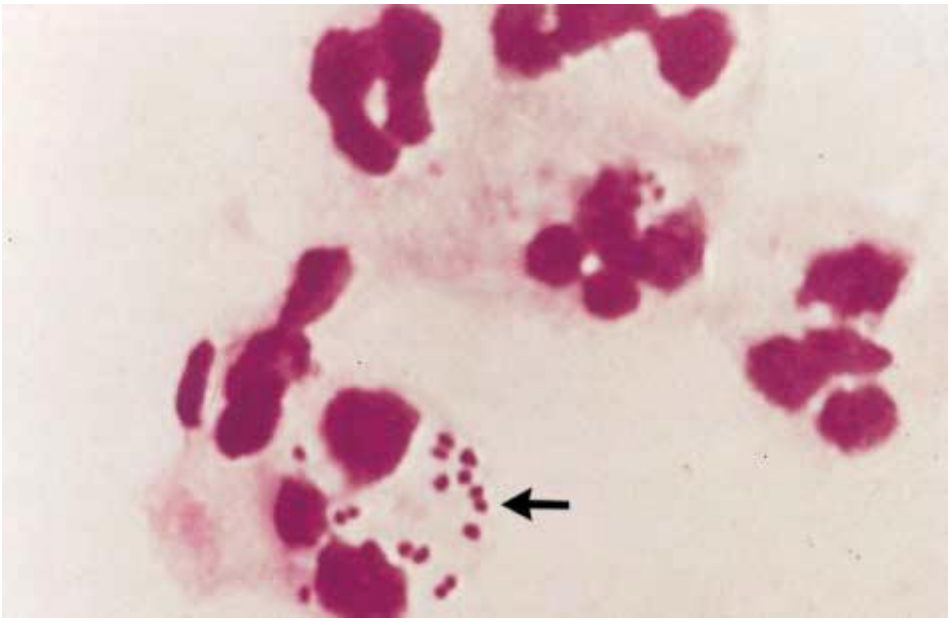


Figure 1 *N. meningitidis* (Arrow) in Cerebrospinal Fluid (Gram's stain, x1000)[1]

Capsular polysaccharide antigens are used to differentiate meningococci into thirteen serogroups.[4] Six of thirteen serogroups (A, B, C, W135, X and Y) can cause clinical disease, such as meningitis, septicaemia or both.[5] In Australia, the majority of IMD cases are caused by serogroup B.[6] The serogroups can be further subclassified into serotypes and serosubtypes by identifying Outer

Membrane or Porin Proteins (OMPs). The serotyping antigens are either the class 2 or 3 OMPs and the serosubtyping antigen is the class 1 OMP.[7] The serogroup, serotype, and serosubtype together are used to describe the phenotype of an organism.[4] In addition to conventional serotyping, genotyping has been increasingly used by sequence typing and sequence determination of *porA*, *porB* and *FetA* genes.[6] Although serotyping is important for developing vaccination strategies, genotyping becomes important to determine the genetic lineage of *N. meningitidis* causing IMD.[8]

2.2 CARRIAGE, TRANSMISSION AND PATHOGENESIS

Humans are the only known host of *N. meningitidis* and the human nasopharynx is the natural reservoir for the bacteria.[9] The bacteria are transmitted from one person to another through aerosol droplets or very close contact with respiratory secretions or saliva, such as through kissing or sharing drinks.[5, 9] The organism often colonises in the human nasopharynx and oropharynx, but can also be found in the oral mucosa, rectum and urogenital tract.[10] Most people become asymptomatic carriers. After a period of colonisation, the organism can be naturally cleared by the human immune system. It is estimated that approximately 10% of the population carry meningococci for weeks to months without the bacteria causing invasive disease.[11] Carriage rates vary between age groups, increasing through childhood from 5% in infants aged less than one year to 8% in children aged ten years, peaking at 24% in young adults aged 19 years, and decreasing to 13% in adults aged 30 years with 8% carriage in 50-year olds. Changes in social behaviour may account for the non-linear carriage trend.[12] A low carriage rate and high level of antibody has been observed in infants, probably due to the antibody being transported across the placenta from their mother's serum during the last six weeks of pregnancy.[11] High carriage prevalence is also found in lower socioeconomic groups and confined or linked populations such as military recruits, pilgrims, college students living in dormitories or prisoners.[8, 12-15] Furthermore, physical damage to the naso-oropharyngeal mucosal surface by smoking, increases the risk of carriage and IMD.[16, 17] Estimates of carriage prevalence are important for understanding the dynamics of carriage and disease and for evaluating the potential effect of vaccination programs, for example herd immunity, namely indirect population protection. The impact of a meningococcal

vaccine on the acquisition of meningococcal carriage or on existing carriage, has been considered as a vital determinant of the indirect population protection in economic evaluation studies.[18, 19]

The mechanisms leading from colonisation to invasive disease are not fully understood. The invasion is thought to be a consequence of meningococcal virulence factors, environmental and social conditions and host susceptibility such as previous or concomitant viral infections, the status of host immune system and levels of serum antibodies which can activate complement-mediated bacteriolysis and/or opsonophagocytosis.[5, 8, 12] Patients with complement deficiency have an increased risk of IMD.[9] History of preceding illness, intimate kissing, being a university student and a preterm birth have been observed to be independent risk factors in adolescents.[20] Although people can carry the organism for weeks to months, IMD is more likely to occur within the first week after the acquisition of a pathogenic meningococcal strain.[5, 8] The majority of IMD cases are caused by strains from a small number of hypervirulent genetic lineages with almost 90% of pharyngeal carriage isolates not associating with IMD due to non-pathogenicity.[10] It was found the strains responsible for IMD are always encapsulated, which supports the assumption that the meningococcal capsule is an important virulence factor.[21] The bacterial polysaccharide capsule prevents the organism from being killed by the normal human immune system.[8, 9] Following invasion, circulating levels of endotoxin (lipopolysaccharide), bacterial load and host characteristics are associated with the severity and different forms of IMD.[5] For example, the release of bacterial toxin activates the complement cascade which results in disseminated intravascular coagulation (DIC) with microvascular thromobosis. At

the next stage, peripheral ischaemia and skin and subcutaneous necrosis can affect the extremities such as the digits, nose and genitals while many require local debridement or amputations.[22] In the severe cases, ischaemia can progress and involve the whole limb requiring amputations. In addition, there is the possibility of septicaemic shock due to loss of circulating plasma volume.[23]

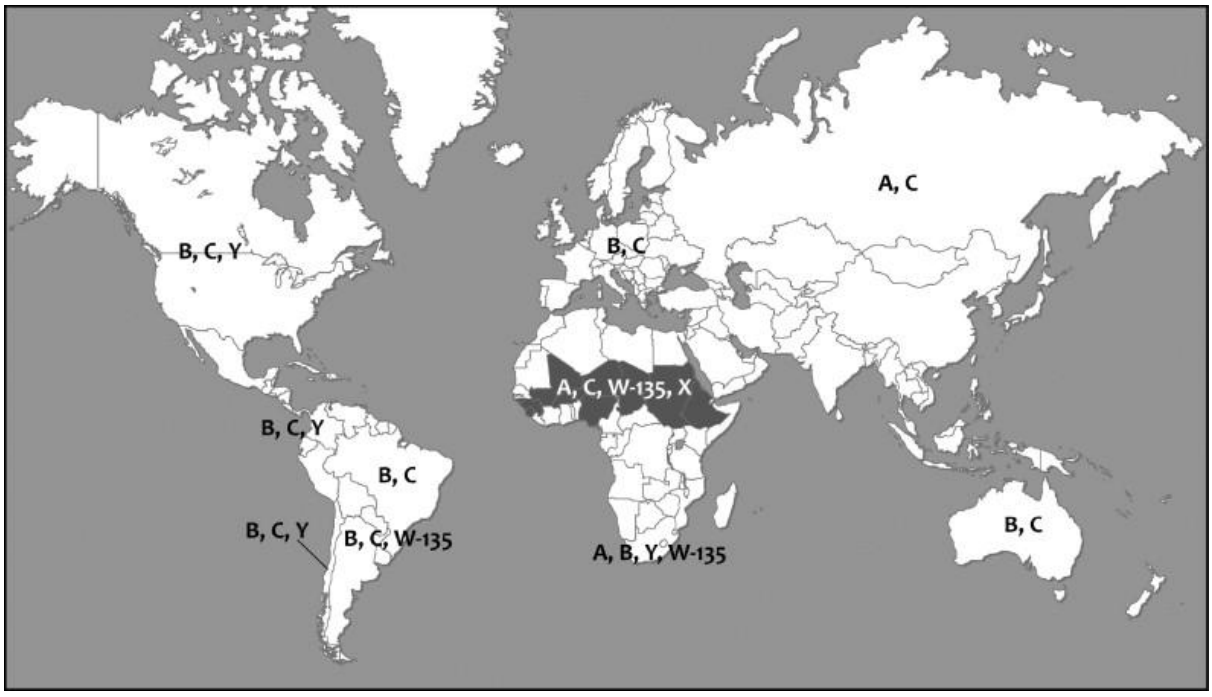
Once the organism has crossed the blood-brain barrier, invaded the meninges and entered the subarachnoid space, meningococci multiply uncontrolled due to lack of humoral and cellular host defence mechanisms.[24, 25] The evolving endotoxin release activates the meningeal inflammatory process and subsequently results in development of meningitis.[8] Brain inflammation causes raised intracranial pressure and blocked cerebral perfusion which can lead to brain and central nervous system malfunction.[26] It was reported that 8 to 20% of survivors following meningococcal meningitis can have neurological sequelae such as sensorineural deafness, seizures and mental retardation.[27-32]

2.3 EPIDEMIOLOGY AND SEROGROUP DISTRIBUTION

2.3.1 Global epidemiology and serogroup distribution

N. meningitidis is the leading infectious cause of death in childhood in industrialised countries despite advanced medical treatment.[33] Among 13 diverse polysaccharide capsule determined serogroups, A, B, C, W135 and Y are responsible for most cases of IMD with X strains only causing the disease in Africa.[34] In the US, the majority of IMD cases are caused by serogroup Y, C and B. Serogroup B has prevailed in other industrialised countries such as Australia and the European Union following introduction of a successful universal meningococcal C vaccination program.[5] Sub-Saharan Africa, known as the African meningitis belt, has the highest incidence of serogroup A IMD. A general estimation of worldwide distribution of serogroups causing IMD is shown below.[21]

Figure 2: Worldwide distribution of serogroups causing IMD[21]



IMD is generally endemic in developed countries but has been epidemic in Sub-Saharan Africa.[9] Infants aged less than one year have the highest incidence of IMD,[35] the reason for which is not well understood and may be due to immaturity of the immune system and lack of acquired serum bactericidal antibodies. Adolescents and young adults have a secondary peak of disease, likely attributable to changes in social behaviours such as social interactions and sharing accommodation.[5, 21] Although the incidence is low especially in developed countries and improvements have been made in antibiotic treatment protocols, the case fatality rate still remains at 7 – 11% [36, 37] with 11–19% of IMD survivors developing serious sequelae such as amputations required following disseminated intravascular coagulation and purpura fulminans, and neurologic deficits including deafness as a result of meningitis.[30, 38, 39] Up to 57% of survivors have reported short or long term sequelae.[40-43] Moreover, a study in Denmark observed that following the acute phase of IMD, survivors had an increased long-term mortality, which resulted mainly from central nervous system diseases.[44] Infants and older patients were reported to have higher case fatality rates.[45, 46]

Capsular switching, antigenic changes, age, ethnic minority, low socioeconomic status, climactic conditions, recent or concomitant upper respiratory infection, behavioural risk factors and living conditions are believed to be associated with changes in the epidemiology of IMD.[21] When a new meningococcal vaccination program is universally introduced, against a certain serogroup but not all major serogroups, serotype replacement could potentially occur with an increased incidence of serotypes or serogroups which are not covered by the vaccines.

2.3.2 Epidemiology in Australia

In Australia, IMD has been a notifiable disease since 1991. IMD has a seasonal pattern with a peak incidence in winter and spring.[6, 47] The national surveillance data of IMD between 2005 and 2007 showed that the highest notification rate occurred in children aged 0 to 4 years (8.4 per 100,000 population) and a second peak in the adolescents and young adults aged 15-24 years (3.1 per 100,000 population) with a slight male preponderance. Infants aged less than one had the highest notification, hospitalisation and death rates (19.4 notifications, 34.4 hospitalisations, 2.0 deaths per 100,000 population) within the 0 – 4 years old age group.[48] Since the meningococcal C vaccination program was implemented in Australia in 2003, the number of notifications has dropped from 687 in 2002 to 223 in 2012. Approximately 200 – 300 cases of IMD were notified each year in Australia within the last five years, with the highest number of notifications occurring in New South Wales followed by Queensland, Victoria, South Australia, Western Australia, Tasmania, the Australian Capital Territory and the Northern Territory.[49]

However, the highest notification rates were in South Australia (1.8 per 100,000 population) followed by the Northern Territory (1.7 per 100,000 population) with the lowest notification rate (0.3 per 100,000 population) occurring in the Australian Capital Territory in 2012.[50] There is a continuing decrease in the notification rate in the Northern Territory, which had the highest notification rates between 1994 and 2009. In South Australia, the notification rates have been stable and have varied between 0.8 and 1.8 per 100,000 population during the past twenty

years.[50] It has been estimated that the case fatality rate is 7 – 8% in Australia [21, 51] with the lowest proportion of deaths among the hospitalised cases in the 5 – 24 year old age group (1%) and highest in those aged ≥ 60 years (6%).[48]

2.3.3 Impact of vaccination in Australia

Since the introduction of a universal meningococcal C vaccination program in 2003, the notification rate of serogroup C IMD has declined with meningococcal B disease considerably predominating. In 2002, although most serogroup-confirmed IMD cases were caused by serogroup B (63%, n=210) in total, serogroup C infection accounted for 41% of IMD cases and dominated in Victoria (56%), Tasmania (70%) and the Australian Capital Territory (80%).[52] In 2011, out of a total of 241 laboratory-confirmed cases, 84% (n=179) of serogroup-confirmed IMD cases were caused by serogroup B infection with 9 cases of serogroup C (4%), 11 cases of serogroup W135 (5%), and 15 cases of serogroup Y cases (7%). The number of serogroup C cases has decreased with an increase in serogroup B and Y infection. No cases of serogroup C IMD were reported for children aged less than 19 years nationally. Moreover, there were no cases of serogroup C infection in 2011 in Western Australia, the Australian Capital Territory and the Northern Territory with less than 10% of IMD cases caused by serogroup C in other states: 9% in South Australia, 2% in Victoria, 10% in Tasmania, 4% in New South Wales and 5% in Queensland. In South Australia, 81% of serogroup-confirmed meningococcal cases were caused by serogroup B infection. Genotyping results were available for 60% of IMD cases in 2011 showing that the following *porA* genotypes predominated among serogroup B cases: P1.7-2,4 (n=25), P1.7,16-26 (n=20), and P1.22,14-6 (n=16).[6] In general, serogroup B meningococci are of

heterogeneous phenotypes, but are also challenging to characterise by serological methods and some could not be phenotyped. Phenotype B:15:P1.7 has been circulating in Australia for years and the other main phenotype is B:4:P1.7.[6, 52]

2.4 CLINICAL MANIFESTATIONS

N. meningitidis can cause bacteraemia without sepsis, meningococcemia alone, meningitis alone or with meningococcemia, and chronic infection.[5] After a pathogenic organism enters the blood stream, the presence of the organism is called bacteraemia. The organism can then multiply and spread in the blood stream, known as meningococcal septicaemia or meningococcemia. Meningitis is inflammation of the meninges, which can be caused by bacteria, viruses, or parasite, and by other non-infectious agents. *Streptococcus pneumonia, Haemophilus influenzae,* and *N. meningitides* are the main causes of bacterial meningitis.[53] Clinical symptoms and signs of meningococcal meningitis alone are indistinguishable from other bacterial meningitis.[5]

IMD usually develops within one week following acquisition of the bacteria with an incubation period of 3 to 4 days and a range of 2 to 10 days.[5, 54] Initial symptoms may be nonspecific or similar to a viral upper respiratory tract infection.[55] Meningitis is the most common presentation of IMD and is caused by haematogenous spreading of the bacteria.[9, 54] Classic cerebral symptoms include neck stiffness, photophobia, irritability, seizures, vomiting and intense headache.[1] Because the meningococcus has a propensity to invade the meninges, patients may have meningitis clinically with negative blood culture or serology results.[8] Neurological deficits such as deafness, cerebral infarction, subdural effusion or empyema, brain abscess, ataxia, blindness, cranial nerve palsies, hemiparesis and obstructive hydrocephalus, can occur following meningitis mainly due to inflammation in the subarachnoid space.[5, 39] In case of meningococcal septicaemia (or meningococcemia), a fever and maculopapular,

purpuric or petechial rash appear. The non-blanching haemorrhagic rash is the most distinctive feature of meningococcal septicaemia. Fulminant meningococcemia may develop within a few hours and rapidly progress to septic shock characterised by petechial or purpuric rash, hypotension, DIC, acute adrenal haemorrhage, and multiorgan failure and coma. Acute complications include skin necrosis, dry gangrene of extremities, adrenal haemorrhage, arthritis, endocarditis, pericarditis and renal failure associated with vasculitis, DIC and hypotension. Growth plate damage and later skeletal deformities may also result from DIC.[5] Acute septicaemia with or without meningitis can be severe and is associated with poorer prognosis and greater mortality compared with meningococcal meningitis.[56]

It is estimated that meningitis occurs in 80 – 85% of IMD cases with meningococcemia in 5 – 20% of patients.[57] 5 – 15% of IMD patients can present with pneumonia.[53] Much less frequently, meningococcal infections can also cause pericarditis, otitis media, epiglottitis, conjunctivitis, urethritis and arthritis.[58] Chronic meningococcemia, characterised by prolonged and intermittent fever, rash, joint pain and headaches, can occur but is relatively rare.[59]

Long term sequelae occurring in approximately 10 – 20% of survivors following IMD include hearing loss, disabling motor impairment resulting from amputations, visual impairment, seizures and severe communication disabilities.[43, 54]

2.5 CLINICAL AND PUBLIC HEALTH MANAGEMENT, PREVENTION AND VACCINES

During the 18th century, IMD was associated with a very high case fatality rate. In this pre-antibiotic era, more than 70% of IMD patients died without any antibiotic treatment.[60] In the UK, IMD has been legally notifiable since 1912 and case fatality rates varied between 95% and 61% between 1912 and 1937.[61] Epidemiologic investigation in military camps found that overcrowding was associated with an increase in IMD incidence. The incidence of IMD in military camps declined significantly after the space between beds was increased and indoor ventilation improved.[60] Prior to the introduction of antibiotic treatment with sulphonamides, meningococcal antisera had been used intrathecally and demonstrated some treatment effects, lowing case fatality rates to less than 30%.[60, 61] Since the antibiotic treatment of sulphonamides was available from 1932, case fatality rates dropped to approximately 10%.[61, 62] However, sulphonamide-resistant epidemics were observed just a few years after discovery of sulphonamides.[63] Currently, parenteral antibiotics including benzylpenicillin or ceftriaxone are required to be given to patients with suggestive meningococcal symptoms or signs by general practitioners prior to hospital admission. IMD patients should receive a 3 to 5 day treatment of benzylpenicillin, ceftriaxone and cefotaxime after admission. Clearance antibiotics and vaccination should also be offered to close contacts of IMD cases.[64] The clearance antibiotics are aimed to stop carriers transmitting the bacteria again and infecting more people. Contrary to public belief, individuals with IMD are not effective transmitters.[65]

Four types of MenC vaccines are currently available in Australia:

- meningococcal C conjugate vaccines (MenCCV):
    - Meningitec – Pfizer Australia Pty Ltd (meningococcal serogroup C–CRM197 conjugate)
    - Menjugate – CSL Limited/Novartis Vaccines and Diagnostics Pty Ltd (meningococcal serogroup C–CRM197 conjugate)
    - NeisVac-C – Baxter Healthcare (meningococcal serogroup C–tetanus toxoid conjugate)
- Haemophilus influenzae type b–meningococcal C combination vaccine (HibMenCCV):
    - Menitorix – GlaxoSmithKline (Haemophilus influenzae type b (PRP-T)-meningococcal serogroup C–tetanus toxoid conjugate)
- quadrivalent meningococcal conjugate vaccines (4vMenCV):
    - Menactra – Sanofi Pasteur Pty Ltd (meningococcal serogroups A, C, W135, Y–diphtheria toxoid conjugate)
    - Menveo – CSL Limited/Novartis Vaccines and Diagnostics Pty Ltd (meningococcal serogroups A, C, W135, Y–CRM197 conjugate)
- quadrivalent meningococcal polysaccharide vaccines (4vMenPV):
    - Mencevax ACWY – GlaxoSmithKline (meningococcal serogroups A, C, W135 and Y polysaccharides)
    - Menomune – Sanofi Pasteur Pty Ltd (meningococcal serogroups A, C, W135 and Y polysaccharides)

According to the Australian Immunisation Handbook, only routine vaccination with MenCCV or Hib-MenCCV is recommended for children at the age of 12 months.[66] Herd immunity has been observed following implementation of the

universal Men C vaccination in the UK with both carriage rates in adolescents and attack rates among unvaccinated children declining by 67%.[67, 68]

The first MenB vaccine, Bexsero®, for protection against endemic serogroup B disease, has recently been approved in the EU and Australia and is currently being considered for inclusion in the National Immunisation Program in Australia and the UK.[69] Vaccine development against serogroup B disease has been slow due to difficulties in identifying an appropriate vaccine candidate. Previous Men B vaccines using OMP can only provide protection against the epidemic strain.[70] Due to similarity between serogroup B capsular polysaccharide antigen and the human neural cell adhesion molecules, non-capsular-based vaccines are required to prevent serogroup B IMD.[71] A capsular Men B vaccine study in adults showed the antibodies induced were not functional.[72] Consequently, Men B vaccine research has focused on cell-surface protein antigens contained in outer-membrane vesicles (OMV).[73] The new Men B vaccine contains four main immunogenic components, three novel antigens combined with OMV from the New Zealand epidemic NZ98/254 strain.[74] Another bivalent vaccine is being developed and based on two factor H-binding proteins.[70, 73, 75-78] However, the protection of new Men B vaccines against carriage is uncertain, which is a key determinant of the herd immunity and important for cost-effectiveness considerations.[18] The potential indirect population protection can considerably reduce disease burden and impact cost-effectiveness results significantly.[19] Previous serogroup B OMP vaccines did not demonstrate any effect on reduction of carriage rate.[79-81] The new MenB vaccine is recommended and licenced for

prevention against serogroup B disease in children and adults from 2 months of age.[69]

2.6 CLINICAL BURDEN

Up to 57% of survivors may develop permanent sequelae following IMD.[35, 40-43, 53] Serogroup C infection has previously been shown to be associated with a higher complication or sequelae rate, but results from different studies are inconsistent.[30, 35, 40, 82, 83] Meningitis can cause hearing impairment, neurological deficits, seizures, behavioural difficulties, and/or visual impairment.[12] In addition to amputations resulting from ischaemic limbs during the acute admission, septicaemia can have long-term consequences such as skin scarring, leg length discrepancy, angular deformity and distorted body disproportion and chronic pain.[12, 22] The outcome of septicaemia is often more severe than meningitis with a higher case fatality rate.[38]

With earlier diagnosis and prompt treatment, outcomes for most children who are diagnosed with IMD are good. If the patient makes an uncomplicated recovery then they can be discharged into the care of their general practitioner. However symptoms of fatigue and headache may persist for months after the acute illness. The guidelines for early clinical and public health management of meningococcal disease in Australia suggest that if a patient had evidence of nerve damage or impaired conscious level at any stage during the illness then they will require at least one outpatient review that includes a follow-up of brain and nerve function. As deafness is the single most common permanent deficit in survivors of meningococcal meningitis, occurring in 4% of survivors [84] and is more common in children than adults,[4] the current guidelines suggest that an auditory review in an outpatient clinic should be made for all meningococcal meningitis survivors. Furthermore, a significant proportion of survivors can have tissue damage

requiring surgical treatment that may include skin grafts, and a partial or complete amputation of limbs. When an amputation is required, the patient will need assessment and follow-up physiotherapy in an outpatient clinic following discharge from hospital. For patients with sequelae, long-term clinical management and social support are required from health professionals, physiotherapists, special education services and social workers.

Complications and sequelae of survivors following IMD were reviewed in a number of studies. A global systematic review indicated the median risk of at least one major sequelae following meningococcal meningitis was 7.2% (IQR: 4.3-11.2%).[53] Furthermore, a systematic review of sequelae following bacterial meningitis in Africa suggested 7% of patients with meningococcal meningitis had neuropsychological sequelae at the time of discharge from hospital.[85] In Houston, 86 children admitted with IMD between 1977 and 1979 were prospectively assessed with results demonstrating 27% of survivors developed complication and sequelae.[29] In Quebec, a retrospective survey assessed the outcomes of laboratory confirmed IMD cases between 1990 and 1994 and reported a case fatality rate of 11.5% with a higher rate of sequelae in survivors of serogroup C disease.[30] Another surveillance study also conducted in Canada between 2002 and 2011, showed that children had a slightly higher sequelae rate than adults with an overall sequelae rate of 19%.[35] A prospective, matched-cohort study in the UK examined the physical, neurocognitive, social and psychological outcomes of IMD cases in adolescence.[40] In addition to a high sequelae rate (57%), lack of medical follow-up, lower educational attainment, less social support, greater depressive symptoms, significant reduction in quality of life

and chronic fatigue were observed in this study. Moreover, another case-control study (MOSAIC) evaluating outcomes of serogroup B IMD in children and adolescents in the UK, reported 36% of survivors had physical, cognitive and/or psychological deficits.[43]

The existing literature on outcomes from IMD is limited, particularly in relation to Australian data. IMD has been a notifiable disease since 1991. Surveillance of this disease within Australia is carried out by the National Notifiable Disease Surveillance System (NNDSS) with additional laboratory surveillance completed by the National Neisseria Network (NNN). The NNN provides the means to type different meningococcal bacteria including serogroup, serotype and serosubtype. Outcome data from the NNN, the national reporting system for IMD is only available for 25 of 241 cases of laboratory confirmed IMD in Australia during 2011,[6] showing a paucity of information about deaths and sequelae from IMD. The NNN was established primarily to concentrate on and coordinate meningococcal strain characterisation and differentiation and collect basic demographic details such as age of individuals but not to collect detailed clinical features and outcomes. No studies have been conducted in Australia to assess the outcomes of disease since introduction of the meningococcal C vaccine program in 2003. This resulted in a decline in IMD due to the “C strain”. However, IMD due to serogroup B accounts for the great majority of meningococcal disease in developed countries.

Since Hansman reported the serogroup and epidemiology of meningococcal disease from 1971 to 1980, no studies have analysed clinical characteristics,

serogroup data and outcomes in South Australia.[51] A retrospective five year case review study of IMD cases in Western Australia between 1990 and 1995 reviewed outcomes such as death or sequelae (including hearing loss, scarring and limb loss).[86] The study identified 105 children aged less than 14 years of age with results showing 1% had hearing loss, 4.8% had skin defects and 2.9% required amputations. Therefore, a total morbidity rate of 8.6% with a case fatality rate also of 8.6% was reported. However, serogroup subanalyses were not performed. An audit conducted in the Hunter New England Area reviewed IMD notifications between 2005 and 2006.[87] The study was not specifically investigating sequelae however the authors identified 24 notified cases resulting in one death and another with multiple limb amputations. The study also identified seven cases attributable to the meningococcal C infection. A long term follow-up of survivors who had experienced bacterial meningitis in childhood was reported in the year 2000.[88] The study retrospectively identified a cohort of 166 children aged 3 months to 14 years admitted to the Royal Children's Hospital, Melbourne between 1983 and 1986. The follow-up evaluations were performed between 1991 and 1993. Grade and sex-matched controls were recruited. This case-control study indicated 8.5% of bacterial meningitis survivors had major neurological, auditory or intellectual impairments. A further 18% of survivors had an attributable risk for minor impairment. These data are now well out-of-date and not relevant to the current situation in Australia, where different meningococcal serogroups now predominate.

2.7 ECONOMIC BURDEN

To the best of our knowledge, costing studies have not been conducted in Australia. Costs of hospitalisation are a major component of health service consumption [41, 42, 89] and are imperative in estimating the overall direct cost burden of IMD.

A number of studies estimating the direct costs of meningococcal disease have been conducted in the US. Direct hospital costs of 1654 IMD cases admitted between 1999 and 2001 were analysed by age group in a US costing study.[90] It was concluded that IMD had considerable economic and clinical consequences for patients in all age groups with a mean length of stay (LOS) of 9 days and an average cost per hospitalisation of US$ 23,294. Infants had the lowest average cost with the high cost occurring in adolescents. However, the costing data were not adjusted by socio-demographic factors and the sample was not representative. In another US costing study, the costs of acute hospitalisation and follow-up care up to one year from 1999 to 2007, were estimated retrospectively by using three administrative hospital or commercial insurance databases.[89] Their results indicated the follow-up costs (average: US$ 21,682) were mainly driven by repeat hospitalisations with a mean facility cost of approximately US$ 20,000 and a mean LOS of 8 – 9 days per initial stay. Only unadjusted results were reported in this study. Two studies selected patients admitted with IMD from 1997 or 1998 to 2009 from two different administrative insurance databases, and compared total health care costs including acute admissions, readmissions, outpatient visits and medications between patients with and without sequelae.[41, 42] The study results revealed that risk-adjusted total costs during the one year follow-up period were

almost two or three times higher in patients with sequelae than those without sequelae. The adjusted risk of readmissions was 1.7 times higher for patients with sequelae. A retrospective case-control study estimating inpatient costs, LOS and mortality in children and adolescents up to 20 years of age in 2006, found that the length of hospital stay and the costs of hospitalisation were highest for infants under 12 months of age with a mean LOS of 9 days and a mean admission cost of US$ 36,454 (1.9 days and US$ 5,401 for controls).[91] All patients in the above mentioned studies were selected using the International Classification of Diseases (ICD) diagnosis codes and were not verified against laboratory results or hospital records. The authors acknowledged that coding errors may have resulted in underestimation or overestimation.

In the UK, a costing study estimated the lifetime costs of treatment of acute infection and management of long-term sequelae by developing two severe case scenarios of meningitis and septicaemia based on systematic reviews of the literature, interviews with IMD survivors and their families, and discussion with clinicians.[92] However, the estimated costs may not represent the real costs as the quantity of resource input was generated in consultation with experts.

Indirect costs were estimated in a meningitis study in Africa.[93] Seventeen percent of 66 children enrolled in the study were diagnosed with IMD. Ninety percent of meningitis related household costs incurred were due to productivity loss. Recall bias limited generalisability of the study results, as all costing data were collected retrospectively through interviews and questionnaires and the

productivity costs were envisaged by caregivers rather than real loss in productivity.

As previous research data were not stratified by serogroup due to lack of serogroup data, the impact of meningococcal B serogroup disease has not been assessed, revealing a knowledge gap about healthcare resource consumption associated with serogroup B disease. Moreover, the cost of illness studies from overseas may not be representative of costs incurred in Australia due to differences in serogroup distribution, patient characteristics and market value of medical goods and services.

Cost of illness studies can produce reasonable estimates of the real economic consequence of a specific disease [94] and help us to understand the importance of a particular health problem.[95] Costing studies are needed to provide a rough estimation of the cost saving and the medical benefits to inform public funding decisions such as vaccination programs.[96] A published review of the economic evaluation of meningococcal vaccine programs indicated that long-term outcomes of the disease and health care management costs of permanent sequelae were important determinants of potential cost-effectiveness and often not contemplated.[97] It has been recognised that the potential benefits of the meningococcal vaccination program could be undervalued if the costs of long-term management of sequelae following the acute infection were disregarded.[98] These key parameters of economic evaluations including length of stay in hospital, proportions and length of stay of Intensive Care Unit (ICU) admissions and costs associated with sequelae following IMD, received little attention in a number of

previous cost-effectiveness studies of meningococcal vaccination programs.[99-104] A recent economic evaluation study of MenB vaccination, making the assumption about long term costs of managing sequelae (£500 and £10,000 per year per individual for survivors with mild and severe sequelae respectively), has acknowledged limited data available to estimate some important parameters such as the proportion, severity and costs related with sequelae.[19]

2.8 COMMUNITY KNOWLEDGE AND AWARENESS

Previous studies have indicated that parents' perception of disease severity and susceptibility to disease could play an important role in parental acceptance of a relevant vaccine.[105-107] Lack of disease specific knowledge could lead to poor compliance with new vaccines.[108-111] Improving community knowledge of IMD is a priority. Furthermore, high coverage of a vaccine with potential indirect population protection could impact cost-effectiveness results significantly [19] and would also be an important consideration in vaccine funding decision-making. The JCVI in the UK have taken account of the potential for indirect population protection in evaluation of the new Men B vaccine.[18]

There is limited information regarding community, parental and adolescent knowledge and awareness of meningococcal disease, especially in Australia. An online survey was administered in seven countries including Australia to investigate health care providers' and parents' knowledge of and attitudes toward vaccine-preventable disease and introduction of new vaccines in infants, using the new Men B vaccine as an example.[112] Parents who had at least one infant aged 0 – 23 months and health care providers with regular vaccination experience were recruited. The study revealed that 55% of parents recognised that IMD could lead to death and 63% agreed that IMD could cause permanent sequelae with only 16% knowing correctly that infants one year of age had the highest risk of IMD. The study suggested that improving awareness of the vaccine-preventable disease would be important for a successful vaccination campaign. The authors acknowledged that parents with higher socioeconomic status could be more likely to have completed the survey, which would limit generalisability of the study

results. In addition, online surveys are inherently biased as the study population does not reflect the community diversity. In Auckland, a survey was undertaken to assess parental awareness of IMD and measles and attitudes to relevant vaccines in three primary schools in 2002 during an epidemic of serogroup B meningococcal disease.[113] The majority (94%) believed that IMD could be a severe disease for young children. Due to a low response rate (24%) and small sample size (n=188), generalisability of the study results is limited. In a large survey study in the Netherlands (n=1763), parents were invited to be interviewed during a Men C vaccination catch-up campaign.[114, 115] Parents were provided with an information brochure explaining IMD and meningococcal vaccines before their interviews. After their children received Men C vaccine, interviews were conducted. The study results showed a higher perceived vulnerability was associated with a more positive attitude toward the vaccine campaign. However, selection bias is likely, because only parents with vaccinated children were interviewed. All these studies only assessed parental knowledge and attitudes to IMD. The general public's and especially adolescents' views were unknown. Since adolescents have an increased risk of meningococcal infection with a high carriage rate, they are a target group for introduction of Men B vaccination. Evaluating adolescents' understanding and concern about IMD is important and can assist policymakers and immunisation educators to make appropriate educational programs.

2.9 REFERENCES

1. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. *N Engl J Med*. 2001;344(18):1378-88.

2. Vieusseux M. Mémoire sur la maladie qui a régné à Genève au printemps de 1805. *J Med Chir Pharm*. 1805;11:163–182

3. Weichselbaum A. Ueber die Aetiologie der akuten Meningitis cerebro-spinalis. *Fortschr Med.* 1887; 5:573-583.

4. *Guidelines for the early clinical and public health management of meningococcal disease in Australia* 2007, Communicable Diseases Network Australia, Department of Health and Ageing, Canberra.

5. Kliegman R. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, Pa: Saunders;2011:chap 184.

6. Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2011. *Commun Dis Intell*. 2012;36(3):E251-62.

7. Tsai CM, Frasch CE, Mocca LF. Five structural classes of major outer membrane proteins in Neisseria meningitidis. *J Bacteriol*. 1981;146(1):69-78.

8. van Deuren M, Brandtzaeg P, van der Meer JW. Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clin Microbiol Rev*. 2000;13(1):144-66.

9. Strelow VL, Vidal JE. Invasive meningococcal disease. *Arq Neuropsiquiatr*. 2013;71(9B):653-8.

10. Stephens DS. Biology and pathogenesis of the evolutionarily successful, obligate human bacterium Neisseria meningitidis. *Vaccine*. 2009;27 Suppl 2:B71-7.

11. Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(12):853-61.

12. Pace D, Pollard AJ. Meningococcal disease: clinical presentation and sequelae. *Vaccine*. 2012;30 Suppl 2:B3-9.

13. Pether JV, Lightfoot NF, Scott RJ, Morgan J, Steele-Perkins AP, Sheard SC. Carriage of Neisseria meningitidis: investigations in a military establishment. *Epidemiol Infect*. 1988;101(1):21-42.

14. Tappero JW, Reporter R, Wenger JD, Ward BA, Reeves MW, Missbach TS, et al. Meningococcal disease in Los Angeles County, California, and among men in the county jails. *N Engl J Med*. 1996;335(12):833-40.

15. Wilder-Smith A, Barkham TM, Earnest A, Paton NI. Acquisition of W135 meningococcal carriage in Hajj pilgrims and transmission to household contacts: prospective study. *BMJ (Clinical research ed)*. 2002;325(7360):365-6.

16. Stuart JM, Cartwright KA, Robinson PM, Noah ND. Effect of smoking on meningococcal carriage. *Lancet.* 1989;2(8665):723-5.

17. Fischer M, Hedberg K, Cardosi P, Plikaytis BD, Hoesly FC, Steingart KR, et al. Tobacco smoke as a risk factor for meningococcal disease. *Pediatr Infect Dis J.* 1997;16(10):979-83.

18. Joint Committee on Vaccination and Immunisation (JCVI) interim position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health; 2013 [updated 24 July 20132 September 2013]; Available from: https://www.gov.uk/government/publications/jcvi-interim-position-statement-on-the-use-of-bexsero-meningococcal-b-vaccine-in-the-uk.

19. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine*. 2013;31(23):2638-46.

20. Tully J, Viner RM, Coen PG, Stuart JM, Zambon M, Peckham C, et al. Risk and protective factors for meningococcal disease in adolescents: matched cohort study. *BMJ (Clinical research ed)*. 2006;332(7539):445-50.

21. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine.* 2009;27 Suppl 2:B51-63.

22. Monsell F. The skeletal consequences of meningococcal septicaemia. *Arch Dis Child.* 2012;97(6):539-44.

23. Mercier JC, Beaufils F, Hartmann JF, Azema D. Hemodynamic patterns of meningococcal shock in children. *Crit Care Med.* 1988;16(1):27-33.

24. Brandtzaeg P, Mollnes TE, Kierulf P. Complement activation and endotoxin levels in systemic meningococcal disease. *J Infect Dis*. 1989;160(1):58-65.

25. Zwahlen A, Nydegger UE, Vaudaux P, Lambert PH, Waldvogel FA. Complement-mediated opsonic activity in normal and infected human cerebrospinal fluid: early response during bacterial meningitis. *J Infect Dis*. 1982;145(5):635-46.

26. Pathan N, Faust SN, Levin M. Pathophysiology of meningococcal meningitis and septicaemia. *Arch Dis Child*. 2003;88(7):601-7.

27. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J*. 1993;12(5):389-94.

28. Djupesland G, Gedde-Dahl TW. Sequelae of meningococcal disease - studied about six weeks after hospital admission. *NIPH Ann*. 1983;6(1):85-90.

29. Edwards MS, Baker CJ. Complications and sequelae of meningococcal infections in children. *J Pediatr.* 1981;99(4):540-5.

30. Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec, Canada, 1990-1994. *Clin Infect Dis*. 1998;26(5):1159-64..

31. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. *N Engl J Med*. 1990;323(24):1651-7.

32. Schildkamp RL, Lodder MC, Bijlmer HA, Dankert J, Scholten RJ. Clinical manifestations and course of meningococcal disease in 562 patients. *Scand J Infect Dis.* 1996;28(1):47-51.

33. Hart CA, Thomson AP. Meningococcal disease and its management in children. *BMJ (Clinical research ed).* 2006;333(7570):685-90.

34. Boisier P, Nicolas P, Djibo S, Taha MK, Jeanne I, Mainassara HB, et al. Meningococcal meningitis: unprecedented incidence of serogroup X-related cases in 2006 in Niger. *Clin Infect Dis*. 2007;44(5):657-63.

35. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The disease burden of invasive meningococcal serogroup B disease in Canada. *Pediatr Infect Dis J*. 2013;32(1):e20-5.

36. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The impact of childhood meningococcal serogroup C conjugate vaccine programs in Canada. *Pediatr Infect Dis J*. 2009;28(3):220-4.

37. Cohn AC, MacNeil JR, Harrison LH, Hatcher C, Theodore J, Schmidt M, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998-2007: implications for prevention of meningococcal disease. *Clin Infect Dis*. 2010;50(2):184-91.

38. Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J*. 1996 Nov;15(11):967-79.

39. Campsall PA, Laupland KB, Niven DJ. Severe meningococcal infection: a review of epidemiology, diagnosis, and management. *Crit Care Clin*. 2013;29(3):393-409.

40. Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. *Pediatrics.* 2009;123(3):e502-9.

41. Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. *Hum Vaccin.* 2011;7(4):458-65.

42. Karve S, Misurski D, Miller J, Davis KL. Costs of Sequelae Associated with Invasive Meningococcal Disease: Findings from a US Managed Care Population. *Health Outcomes Res Med*. 2011;2:e215-e226.

43. Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. *Lancet Neurol*. 2012;11(9):774-83.

44. Roed C, Omland LH, Engsig FN, Skinhoj P, Obel N. Long-term mortality in patients diagnosed with meningococcal disease: a Danish nationwide cohort study. *PloS one.* 2010;5(3):e9662.

45. Gilca R, Deceuninck G, Lefebvre B, Tsang R, Amini R, Gilca V, et al. The changing epidemiology of meningococcal disease in Quebec, Canada, 1991-2011: potential implications of emergence of new strains. *PloS one.* 2012;7(11):e50659.

46. Bilukha OO, Rosenstein N, National Center for Infectious Diseases CfDC, Prevention. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2005;54(RR-7):1-21.

47. Jelfs J, Munro R. Epidemiology of meningococcal disease in Australia. *J Paediatr Child Health*. 2001;37(5):S3-6.

48. Chiu C, Dey A, Wang H, Menzies R, Deeks S, Mahajan D, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2005 to 2007. *Commun Dis Intell.* 2010;34 Suppl:S50-6.

49. Number of notifications of Meningococcal disease (invasive)*, received from State and Territory health authorities in the period of 1991 to 2012 and year-to-date notifications for 2013 [database on the Internet]. Department of Health and Ageing [cited 8 November 2013]. Available from: http://www9.health.gov.au/cda/source/rpt_4.cfm.

50. Notification Rate of Meningococcal disease (invasive)*, received from State and Territory health authorities in the period of 1991 to 2012 and year-to-date notifications for 2013 [database on the Internet]. Department of Health and Ageing [cited 8 November 2013]. Available from: http://www9.health.gov.au/cda/source/rpt_4.cfm.

51. Hansman D. Meningococcal disease in South Australia: incidence and serogroup distribution 1971-1980. *J Hyg (Lond).* 1983;90(1):49-54.

52. Annual report of the Australian Meningococcal Surveillance Programme, 2002. *Commun Dis Intell*. 2003;27(2):196-208.

53. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(5):317-28.

54. Atkinson W. Epidemiology and prevention of vaccine-preventable diseases: Dept. of Health & Human Services, Public Health Service, Centers for Disease Control and Prevention; 2000.

55. Al-Tawfiq JA, Clark TA, Memish ZA. Meningococcal disease: the organism, clinical presentation, and worldwide epidemiology. *J Travel Med*. 2010;17 Suppl:3-8.

56. Peltola H. Meningococcal disease: still with us. *Rev Infect Dis*. 1983;5(1):71-91.

57. Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Cartter ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. *J Infect Dis*. 1999;180(6):1894-901.

58. Cartwright KA. Early management of meningococcal disease. *Infect Dis Clin North Am*. 1999;13(3):661-84, viii.

59. Gold R. Clinical aspects of meningococcal disease. In: Evolution of meningococcal disease. Volume 11. 1987. Pp: 69–97. Boca Raton, Florida: CRC Press.

60. Frosch M, Maiden MCJ. Handbook of meningococcal disease. Wiley Online Library; 2006.

61. Jubb AA. Chemotherapy and Serotherapy in Cerebrospinal Meningitis. *Br Med J.* 1943;1(4294):501-4.

62. Beeson PB, Westerman E. Cerebrospinal Fever and Sulphonamides. *Br Med J*. 1943;1(4294):497-500.

63. Schoenbach EB, Phair JJ. The sensitivity of meningococci to sulfadiazine. *Am J Hyg*. 1948;47(2):177-86.

64. *Guidelines for the Early Clinical and Public Health Management of Meningococcal Disease in Australia* 2007, Communicable Diseases Network Australia (CDNA), Department of Health and Ageing.

65. Gilmore A, Stuart J, Andrews N. Risk of secondary meningococcal disease in health-care workers. *Lancet*. 2000;356(9242):1654-5.

66. *The Australian Immunisation Handbook* 2013, National Health Medical Research Council, Department of Health and Ageing, Canberra.

67. Maiden MC, Stuart JM, Group UKMC. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. *Lancet*. 2002;359(9320):1829-31.

68. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. *Lancet*. 2001;357(9251):195-6.

69. Novartis Media Relations. Novartis vaccine Bexsero® approved in Australia to help protect against MenB disease, a deadly form of bacterial meningitis. [updated 15 August 2013; accessed 07 October 2013]; Available from: http://www.novartis.com/newsroom/media-releases/en/2013/1723151.shtml.

70. Cohn AC, Harrison LH. Meningococcal vaccines: current issues and future strategies. *Drugs*. 2013;73(11):1147-55.

71. Finne J, Leinonen M, Makela PH. Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine development and pathogenesis. *Lancet.* 1983;2(8346):355-7.

72. Girard MP, Preziosi MP, Aguado MT, Kieny MP. A review of vaccine research and development: meningococcal disease. *Vaccine.* 2006;24(22):4692-700.

73. Marshall HS, Richmond PC, Nissen MD, Jiang Q, Anderson AS, Jansen KU, et al. Safety and immunogenicity of a meningococcal B bivalent rLP2086 vaccine in healthy toddlers aged 18-36 months: a phase 1 randomized-controlled clinical trial. *Pediatr Infect Dis J*. 2012;31(10):1061-8.

74. Carter NJ. Multicomponent meningococcal serogroup B vaccine (4CMenB; Bexsero®): a review of its use in primary and booster vaccination. *BioDrugs.* 2013;27(3):263-74.

75. Richmond PC, Nissen MD, Marshall HS, Lambert SB, Roberton D, Gruber WC, et al. A bivalent Neisseria meningitidis recombinant lipidated factor H binding protein vaccine in young adults: results of a randomised, controlled, dose-escalation phase 1 trial. *Vaccine*. 2012;30(43):6163-74.

76. Marshall HS, Richmond PC, Nissen MD, Wouters A, Baber J, Jiang Q, et al. A phase 2 open-label safety and immunogenicity study of a meningococcal B bivalent rLP2086 vaccine in healthy adults. *Vaccine.* 2013;31(12):1569-75.

77. Nissen MD, Marshall HS, Richmond PC, Jiang Q, Harris SL, Jones TR, et al. A randomized, controlled, phase 1/2 trial of a Neisseria meningitidis serogroup B bivalent rLP2086 vaccine in healthy children and adolescents. *Pediatr Infect Dis J.* 2013;32(4):364-71.

78. Richmond PC, Marshall HS, Nissen MD, Jiang Q, Jansen KU, Garces-Sanchez M, et al. Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents:

a randomised, single-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis*. 2012;12(8):597-607.

79. Bjune G. "Herd immunity" and the meningococcal vaccine trial in Norway. *Lancet.* 1992;340(8814):315.

80. Boslego J, Garcia J, Cruz C, Zollinger W, Brandt B, Ruiz S, et al. Efficacy, safety, and immunogenicity of a meningococcal group B (15:P1.3) outer membrane protein vaccine in Iquique, Chile. Chilean National Committee for Meningococcal Disease. *Vaccine.* 1995;13(9):821-9.

81. Perkins BA, Jonsdottir K, Briem H, Griffiths E, Plikaytis BD, Hoiby EA, et al. Immunogenicity of two efficacious outer membrane protein-based serogroup B meningococcal vaccines among young adults in Iceland. *J Infect Dis.* 1998;177(3):683-91.

82. Healy CM, Butler KM, Smith EO, Hensey OP, Bate T, Moloney AC, et al. Influence of serogroup on the presentation, course, and outcome of invasive meningococcal disease in children in the Republic of Ireland, 1995-2000. *Clin Infect Dis.* 2002;34(10):1323-30.

83. Gottfredsson M, Reynisson IK, Ingvarsson RF, Kristjansdottir H, Nardini MV, Sigurdsson JF, et al. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. *Clin Infect Dis.* 2011;53(9):e117-24.

84. Visintin C, Mugglestone MA, Fields EJ, Jacklin P, Murphy MS, Pollard AJ, et al. Management of bacterial meningitis and meningococcal septicaemia in children and young people: summary of NICE guidance. *BMJ (Clinical research ed).* 2010;340:c3209.

85. Ramakrishnan M, Ulland AJ, Steinhardt LC, Moisi JC, Were F, Levine OS. Sequelae due to bacterial meningitis among African children: a systematic literature review. *BMC Med*. 2009;7:47.

86. Olesch CA, Knight GJ. Invasive meningococcal infection in Western Australia. *J Paediatr Child Health*. 1999;35(1):42-8.

87. Guimont C, Hullick C, Durrheim D, Ryan N, Ferguson J, Massey P. Invasive meningococcal disease--improving management through structured review of cases in the Hunter New England area, Australia. *J Public Health (Oxf)*. 2010;32(1):38-43.

88. Grimwood K, Anderson VA, Bond L, Catroppa C, Hore RL, Keir EH, et al. Adverse outcomes of bacterial meningitis in school-age survivors. *Pediatrics.* 1995;95(5):646-56.

89. Davis KL, Misurski DA, Miller JM, Bell TJ, Bapat B. Cost of acute hospitalization and post-discharge follow-up care for meningococcal disease in the United States. *Hum Vaccin.* 2011;7(1):96-101.

90. O'Brien JA, Caro JJ, Getsios D. Managing meningococcal disease in the United States: Hospital case characteristics and costs by age. *Value Health*. 2006;9(4):236-43.

91. Davis KL, Bell TJ, Miller JM, Misurski DA, Bapat B. Hospital costs, length of stay and mortality associated with childhood, adolescent and young adult meningococcal disease in the US. *Appl Health Econ Health Policy*. 2011;9(3):197-207.

92. Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease : scenarios of severe meningitis and septicemia. *Paediatr Drugs.* 2013;15(1):49-58.

93. Griffiths UK, Dieye Y, Fleming J, Hajjeh R, Edmond K. Costs of meningitis sequelae in children in Dakar, Senegal. *Pediatr Infect Dis J*. 2012;31(11):e189-95.

94. World Health O. Dollars, DALYs and decisions: economic aspects of the mental health system. Geneva: World Health Organization. 2006.

95. Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. *Pharmacoeconomics.* 2011;29(8):653-71.

96. Durand-Zaleski I. Why cost-of-illness studies are important and inform policy. *Vasc Med.* 2008;13(3):251-3.

97. Getsios D, Caro I, El-Hadi W, Caro JJ. Assessing the economics of vaccination for Neisseria meningitidis in industrialized nations: a review and recommendations for further research. *Int J Technol Assess Health Care*. 2004;20(3):280-8.

98. Miller MA, Shahab CK. Review of the cost effectiveness of immunisation strategies for the control of epidemic meningococcal meningitis. *Pharmacoeconomics.* 2005;23(4):333-43.

99. Ortega-Sanchez IR, Meltzer MI, Shepard C, Zell E, Messonnier ML, Bilukha O, et al. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. *Clin Infect Dis.* 2008;46(1):1-13.

100. Scott RD, 2nd, Meltzer MI, Erickson LJ, De Wals P, Rosenstein NE. Vaccinating first-year college students living in dormitories for Meningococcal disease: an economic analysis*. Am J Prev Med*. 2002;23(2):98-105.

101. Shepard CW, Ortega-Sanchez IR, Scott Ii RD, Rosenstein NE. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. *Pediatrics*. 2005;115(5):1220-32.

102. Skull SA, Butler JR. Meningococcal vaccination for adolescents? An economic evaluation in Victoria. *J Paediatr Child Health*. 2001;37(5):S28-33.

103. Trotter CL, Edmunds WJ. Modelling cost effectiveness of meningococcal serogroup C conjugate vaccination campaign in England and Wales. *BMJ (Clinical research ed).* 2002;324(7341):809.

104. Trotter CL, Edmunds WJ. Reassessing the cost-effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model. *Med Decis Making.* 2006;26(1):38-47.

105. Flood EM, Rousculp MD, Ryan KJ, Beusterien KM, Divino VM, Toback SL, et al. Parents' decision-making regarding vaccinating their children against influenza: A web-based survey. *Clin Ther*. 2010;32(8):1448-67.

106. Yarwood J, Noakes K, Kennedy D, Campbell H, Salisbury D. Tracking mothers attitudes to childhood immunisation 1991-2001. *Vaccine*. 2005;23(48-49):5670-87.

107. Bedford H, Lansley M. More vaccines for children? Parents' views. *Vaccine*. 2007;25(45):7818-23.

108. Dorell C, Yankey D, Strasser S. Parent-reported reasons for nonreceipt of recommended adolescent vaccinations, national immunization survey: teen, 2009. *Clin Pediatr (Phila)*. 2011;50(12):1116-24.

109. Hak E, Schonbeck Y, De Melker H, Van Essen GA, Sanders EA. Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program. *Vaccine*. 2005;23(24):3103-7.

110. Ogilvie G, Anderson M, Marra F, McNeil S, Pielak K, Dawar M, et al. A population-based evaluation of a publicly funded, school-based HPV vaccine

program in British Columbia, Canada: parental factors associated with HPV vaccine receipt. *PLoS Med*. 2010;7(5):e1000270.

111. Eppes C, Wu A, You W, Cameron KA, Garcia P, Grobman W. Barriers to influenza vaccination among pregnant women. *Vaccine*. 2013;31(27):2874-8.

112. Bakhache P, Rodrigo C, Davie S, Ahuja A, Sudovar B, Crudup T, et al. Health care providers' and parents' attitudes toward administration of new infant vaccines--a multinational survey. *Eur J Pediatr*. 2013;172(4):485-92.

113. Petousis-Harris H, Turner N, Soe B. Parent views on school based immunisation: A survey of parents of year 1 and 6 in three diverse Auckland schools. *N Z Fam Physician*. 2004;31(4):222-8.

114. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Attitudes and risk perception of parents of different ethnic backgrounds regarding meningococcal C vaccination. *Vaccine*. 2005;23(25):3329-35.

115. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Parents' perceived vulnerability and perceived control in preventing Meningococcal C infection: a large-scale interview study about vaccination. *BMC Public Health*. 2008;8:45.

CHAPTER 3: CLINICAL BURDEN OF IMD IN AUSTRALIAN CHILDREN

The manuscript, “The Clinical Burden and Predictors of Sequelae Following Invasive Meningococcal Disease (IMD) in Australian Children”, reports results of an eleven year audit study of children who were admitted to the WCH in Adelaide between 2000 and 2011 due to IMD. The manuscript was submitted to the Pediatric Infectious Disease Journal and was published as a brief report (see appendix 1).

The existing data on clinical burden of IMD are limited, especially in Australia. The national surveillance report shows the outcome data for IMD are only available for 10% of laboratory confirmed cases in 2011. Since implementation of the meningococcal C vaccination program in 2003, the impact of the current vaccination program on clinical consequences of IMD has not been assessed. Therefore, we aim to evaluate the clinical manifestations, outcomes and sequelae of IMD between 2001 and 2011 retrospectively and investigate predictors of sequelae.

TITLE:

The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children

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NOTE:
Statements of authorship appear on pages 67-68 in the print copy of the thesis held in the University of Adelaide Library.

3.1 ABSTRACT

Background: The aim of this study is to describe the clinical burden of sequelae following Invasive Meningococcal Disease (IMD) in Australian children and identify predictors of sequelae.

Methods: Clinical details were collected from medical records of children admitted to a tertiary paediatric hospital in South Australia with a diagnosis of IMD from 2000 to 2011. Logistic regression was used to identify predictors of sequelae.

Results: Of 109 children hospitalised with IMD, 54.1% were female and 11.9% Aboriginal. The majority of cases were caused by serogroup B (70.6%) with 9.2% caused by serogroup C. Sequelae occurred in 39.2% (40/102) of children with laboratory confirmed IMD; 41.3% (31/75) following serogroup B and 22.2% (2/9) following serogroup C disease (p=0.280). Children with sequelae were more likely to require high level care (70.7%) compared with those without sequelae (45.3%) (p=0.012). For children aged less than one year, sequelae occurred in 100% of children with a history of prematurity compared to 44.4% of full term infants (p=0.038). Independent predictors of sequelae following IMD included: fever ≥ 39°C on presentation to the hospital (OR: 4.5; p=0.012), a diagnosis of septicaemia with meningitis compared to septicaemia alone (OR: 15.5; p<0.001) and meningitis alone (OR: 7.8; p=0.002), and antibiotics given prior to admission (OR: 12.0; p=0.007).

Conclusions: Children with a diagnosis of meningitis and septicaemia and high fever are at increased risk of sequelae. Although IMD is uncommon, sequelae

occur frequently resulting in a high burden of disease, important for Meningococcal B (MenB) vaccine funding considerations.

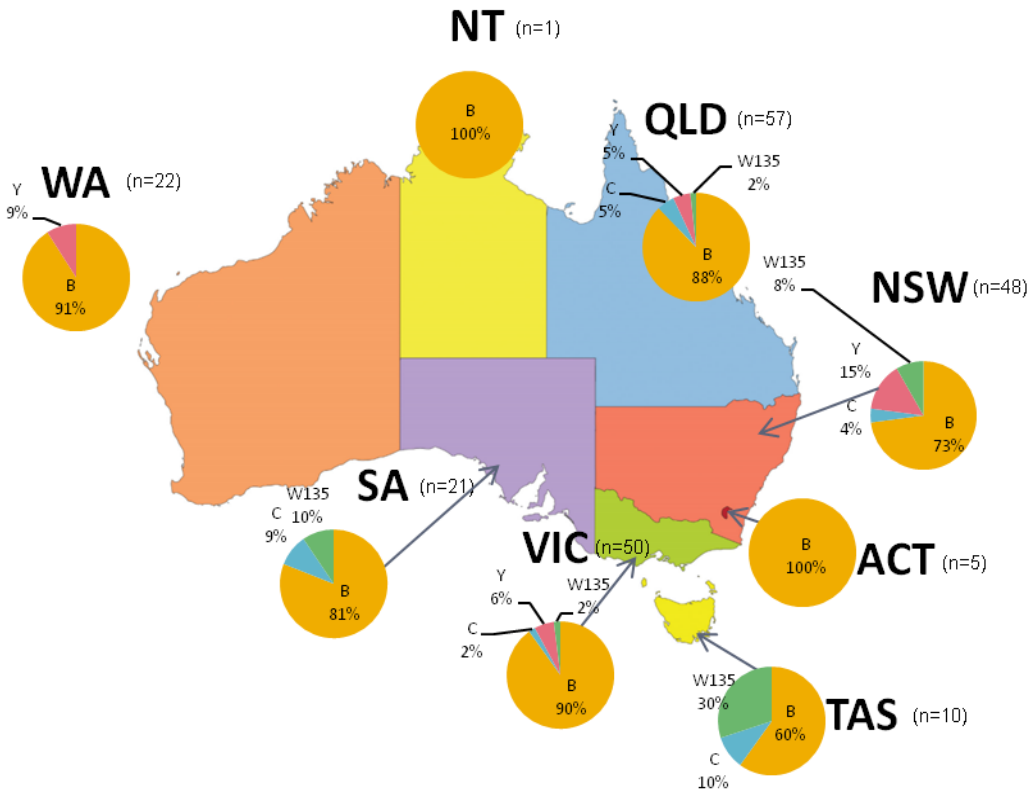
3.2 INTRODUCTION

Invasive meningococcal disease (IMD) has emerged as the most common infectious cause of death in childhood in developed countries.[1] Six of thirteen subgroups (A, B, C, W135, X and Y) of *Neisseria meningitidis* can cause clinical disease.[2] IMD usually manifests as septicaemia, meningitis or both, and is associated with a high case fatality rate of 5–15%.[3, 4] Approximately, 11–19% of IMD survivors experience serious sequelae including amputation, hearing loss, skin scarring and neurological impairment.[5, 6]

In Australia, 4 365 cases of IMD were reported from 2000 to 2011.[7] Since the introduction of the meningococcal C (MenC) vaccine program in 2003 for toddlers at one year of age, the total IMD notification rate in Australia has declined from 2.0–3.5 per 100,000 per year prior to 2004 to 1.0–2.0 per 100,000 population per year from 2004 to 2011. In 2011 in Australia, 83.6% (n=179) of 214 serogroup-confirmed IMD cases were caused by serogroup B (Figure 1).[8]

Figure 1: Serogroup distribution state/territory, Australia

Adapted from Australian Meningococcal Surveillance Programme Annual Report, 2011



Surveillance within Australia is monitored by the National Notifiable Disease Surveillance System (NNDSS) and additional laboratory surveillance is completed by the National Neisseria Network (NNN). The NNN collects data on meningococcal strain characterisation and differentiation and demographic details but does not collect detailed clinical features and outcomes.[8-10]

The outcomes and impact of IMD on Australian children is poorly documented. Outcome data on survival following meningococcal disease (survived or died) is only available for 10% (25/241) of laboratory confirmed cases of IMD notified in Australia during 2011,[8] revealing a knowledge gap about deaths and sequelae resulting from IMD in Australian children. As new meningococcal vaccines including broadly protective meningococcal B (MenB) vaccines are likely to be licensed in Australia very soon, understanding the disease burden of this uncommon but devastating infection is important to direct immunisation policy. The aim of this study is to describe the clinical burden of IMD in South Australian children including clinical features, outcomes and sequelae and determine risk factors for sequelae following IMD.

3.3 METHODS

3.3.1 Setting

The data collection was completed between 27 July 2011 and 28 October 2012 at the Women's and Children's Hospital (WCH) in South Australia. Almost 50% of all ICD coded cases of IMD in South Australian children (< 18 years) were admitted to the WCH during the study period.

3.3.2 Study design and population

The medical records of all children admitted to the WCH with a diagnosis of IMD and aged < 18 years, between May 2000 and April 2011 were reviewed. To identify cases, hospital separation data were accessed to identify any admissions coded with ICD10–A39.0 to A39.9. This was cross checked with laboratory notifications. Both confirmed and probable cases were included in the final analysis. A confirmed case of IMD was defined by isolation of *N. meningitidis* from a normally sterile body site, a positive PCR test, a clinically compatible illness with detection of gram-negative intracellular diplococcic in cerebrospinal fluid (CSF) or in petechiae, a positive IgM test in serum, or a positive antigen test in CSF. Probable cases were defined as a clinically compatible illness diagnosed by the treating physician (and confirmed by two other physicians) with either haemorrhagic rash present or close contact with a confirmed case.[11]

Sequelae were defined as any complications related to IMD that were not resolved at hospital discharge or occurred after discharge.[12]

3.3.3 Data collection and analysis

Medical records were reviewed to collect information about clinical disease, management, complications and sequelae. Specialist and family physician investigations and diagnoses following discharge were captured as completely as possible from the information within the child's hospital medical records. Immunisation history was sourced from the medical records and confirmed on the Australian Childhood Immunisation Register.

The presence or absence of sequelae was the primary outcome measure for the statistical analysis. Variables tested for association with the outcome measures included socio-demographic and clinical indicators (e.g. age, gender, indigenous status, area of residence, respiratory past history, prematurity, diagnosis type, body temperature ≥ 39°C at admission, serogroup and antibiotics received prior to admission). Univariate associations were reported as prevalence estimates and as odds ratios with 95% confidence intervals. A multivariate logistic regression model was developed to identify significant and independent predictors of developing sequelae post IMD infection. Modelling commenced with a fully saturated model, which included the above-mentioned covariates with a p-value of p=0.20 or lower on a univariate analysis of association with sequelae development; non-significant variables were then removed from the model using methods proposed by Hosmer and Lemeshow.[13] All effects were assessed at a 5% alpha level of significance. The analyses were completed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

3.3.4 Ethics

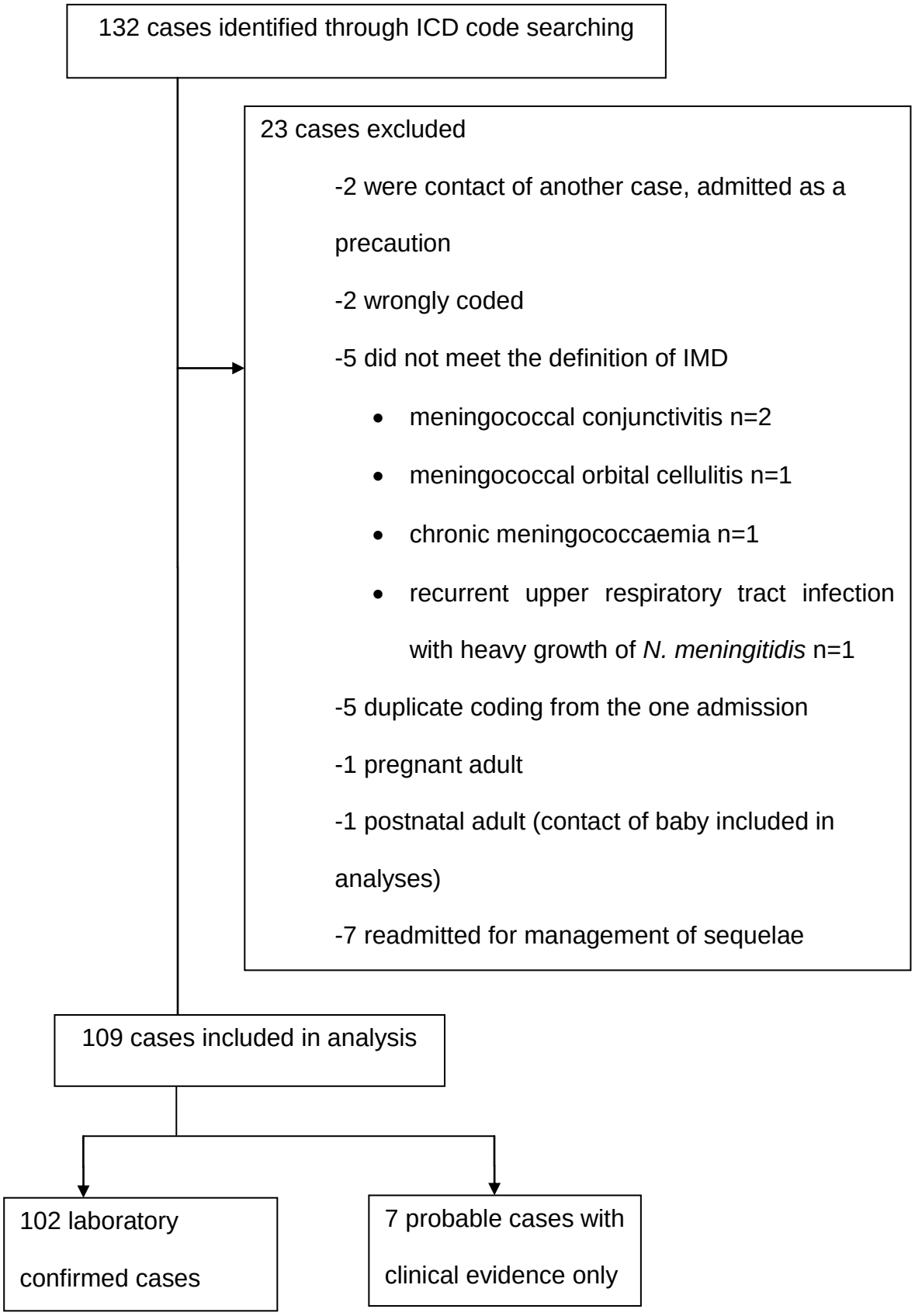
The study was approved by the Women's and Children's Health Network Human Research Ethics Committee.

3.4 RESULTS

3.4.1 Study population

A total of 132 IMD cases were identified. Of these, 23 cases were excluded (Figure 2). Of 109 eligible cases, 102 (93.6%) were laboratory confirmed by PCR, culture, IgM antibody or antigen tests from blood or CSF samples. A further seven (6.4%) were consistent with a clinical diagnosis of IMD, as confirmed by the treating physician and consistent with the definition of probable IMD. Probable cases were included in the data analysis to avoid any omission of IMD cases where a positive laboratory result was not available. There was no statistically significant difference between confirmed and probable cases in the proportion of children developing sequelae (p=0.247).

Figure 2: Cases excluded from cases identified by ICD10 – A39.0 to A39.9 codes



There were more females (54.1%; n=59) than males (45.9%; n=50) with an age range of 22 days to 17 years of age (mean: 3.9 years; median: two years). One third of children were aged less than one year of age and the majority were Caucasian (Table 1).

Table 1: Patient characteristics

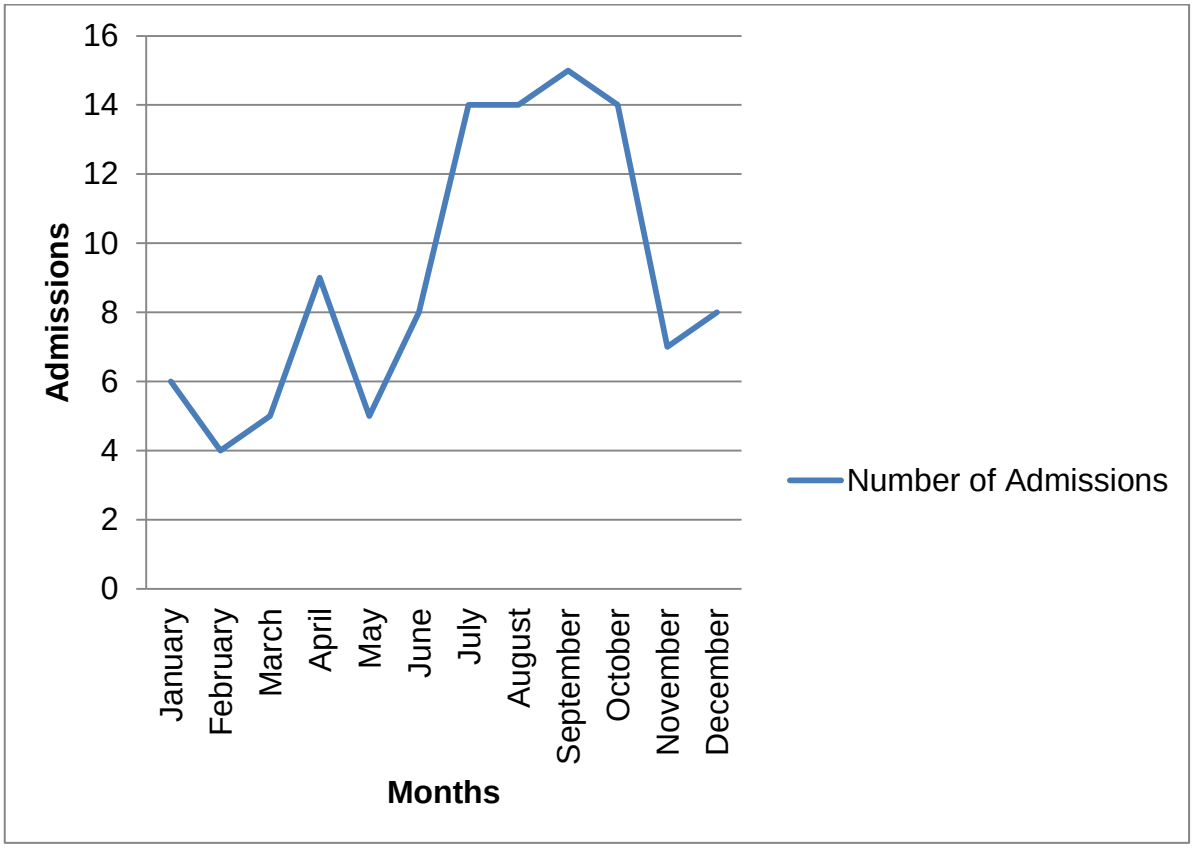
	Overall		Patients with sequelae		Patients without sequelae	
	n	%	n	%	n	%
All Patients	109[#]	-	41	-	64	-
Mean Age (SD)	3.85 (4.53)		3.68 (4.92)		3.86 (4.19)	
Admission Age						
< one year	32	29.4	16	39.0	15	23.4
≥ one year	77	70.6	25	61.0	49	76.6
Sex						
Female	59	54.1	20	48.8	36	56.3
Male	50	45.9	21	51.2	28	43.8
Indigenous Status						
Caucasian	93	85.3	37	90.2	55	85.9
Aboriginal or Torres Strait Islander	13	11.9	3	7.3	7	10.9
Asian	1	0.9	0	0.00	1	1.6
Unknown	2	1.8	1	2.4	1	1.6
Serogroup						
B	77	70.6	31	75.6	44	68.8
C	10	9.2	2	4.9	7	10.9
W135	2	1.8	2	4.9	0	0.0
Y	1	0.9	1	2.4	0	0.0
Unknown*	19	17.4	5	12.2	13	20.3
Previous Medical History						
Absent	73	67.0	26	63.4	45	70.3
Present	36	33.0	15	36.6	19	29.7
Diagnosis Type						
Septicaemia	53	48.6	14	34.2	37	57.8
Meningitis	26	23.9	8	19.5	18	28.1
Meningitis and Septicaemia	30	27.5	19	46.3	9	14.1
Transferred from Other Hospitals						
Not-transferred	55	50.5	18	43.9	37	57.8
Transferred	54	49.5	23	56.1	27	42.2
Residential Remoteness						
Moderately Accessible/Remote	15	13.8	5	12.2	8	12.5
Highly Accessible/ Accessible	94	86.2	36	87.8	56	87.5
Socio-Economic Indexes for Areas (SEIFA)						
High (67^{th} – 100^{th} percentile)	19	17.4	7	17.1	11	17.2
Medium (34^{th} – 66^{th} percentile)	34	31.2	13	31.7	20	31.3
Low (1^{st} – 33^{rd} percentile)	56	51.4	21	51.2	33	51.6
Initial Medical Presentation						
Family Physicians	41	37.6	17	41.5	21	32.8
Emergency Department of Other Hospitals	37	33.9	17	41.5	19	29.7
Emergency Department of WCH	31	28.4	7	17.1	24	37.5
ICU Admission						
No Admission to ICU	68	62.4	18	43.9	50	78.1
Admission to ICU	41	37.6	23	56.1	14	21.9

Inpatient death occurred in two cases and two children were transferred back to rural hospital with unknown outcomes.

* IMD cases with unknown serogroup included 7 probable cases and 12 laboratory confirmed cases.

A seasonal pattern with peak occurrence in late winter and early spring was observed (Figure 3).

Figure 3: Seasonality of IMD admissions by month between May 2000 and April 2011



3.4.2 Clinical features

The most common presenting symptom was rash (76.2%, n=83) which was described as petechial, purpuric or non-blanching. Almost all children (92.7%, n=101), had pyrexia on presentation or a history of pyrexia. The mean temperature on presentation was 38.1°C (range: 35.6–40.5°C). Other symptoms included headache (26.6%, n=29), drowsiness (26.6%, n=29), neck stiffness (27.5%, n=30), joint pain (4.6%, n=5), photophobia (9.2%, n=10) and focal cerebral deficit (1.8%, n=2). Hypotension, defined as systolic blood pressure below the 5th percentile for age [14, 15] occurred in 29 patients (26.6%). Children with hypotension recorded during admission were 2.3 times more likely to develop sequelae than children who were normotensive (p=0.073).

Meningococcal septicaemia and meningitis occurred in 27.5% (n=30) of cases, meningitis in 23.9% (n=26) and septicaemia in 48.6% (n=53) of cases (Table 2). Three children had evidence of co-infection including Influenza A, *Haemophilus influenza b* and H1N1 Influenza.

The median length of admission was six days (range: 1–148 days). Sixteen percent (n=17) required endotracheal intubation either prior to transfer to the WCH or during their admission. In addition, 11.9% (n=13) had a seizure(s) during their admission or on presentation, and 10.1% (n=11) showed focal neurological signs. Just over half of the admissions (56.9%, 62/109) required intensive care unit (ICU) management (37.6%, 41/109) and/or treatment in the high dependency unit (HDU) (27.5%, 30/109). The median length of admission to these units was 29.5 hours (range: 3 to 912 hours).

A physiotherapist was required for 12.8% (n=14) of patients during their hospital admission with 10.9% (n=11) continuing with physiotherapy treatment following discharge. Other allied health support during their hospital stay included speech pathology, dieticians, social work, aboriginal liaison officer assistance and acute pain services. Outpatient services used following discharge from WCH comprised: allergy and immunology, speech pathology, child development, ophthalmology, social work, burns clinic for change of dressings, plastics for review of scars, skin grafts and amputations, orthopaedic clinic for review of amputations and/or metrohome link nurse services to provide the remaining doses of intravenous antibiotics.

3.4.3 Previous meningococcal vaccination

Almost a third (27.5%, n=30) of patients had been previously vaccinated with a MenC vaccine. Of the remaining 79 patients, 24 were too young to receive the vaccine, 32 were admitted prior to the vaccine being available, parents had objected to immunisation for two patients, and 21 had unknown vaccination status or unknown reason for non-vaccination.

Two children with serogroup C disease had previously been vaccinated with a MenC vaccine two or three years before the IMD infection. Both recovered with a short hospital stay (four days for both) with no ICU/HDU admission and no sequelae.

3.4.4 Meningococcal serogroups causing IMD

The majority of cases were caused by serogroup B (70.6%, 77/109), with 9.2% (10/109) caused by serogroup C and for 17.4% (19/109) the serogroup was unknown (Table 2). The majority of serogroup C disease occurred prior to the introduction of MenC vaccine onto the National Immunisation Program in 2003, with only three cases at the WCH due to serogroup C post MenC vaccine introduction.

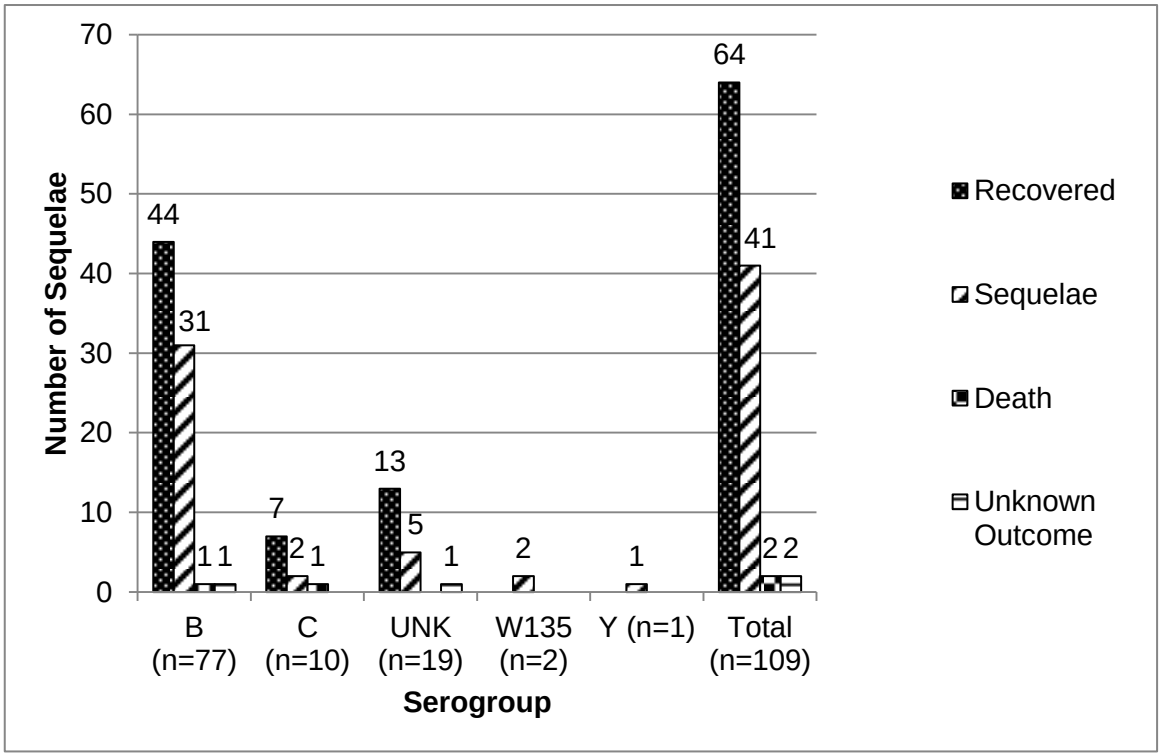
Table 2: Serogroup and diagnosis

	Serogroup										
	B		C		Unknown		W135		Y		Total
Diagnosis	n	%	n	%	n	%	n	%	n	%	n
Meningitis & Septicaemia	25	22.9	0	0	4	2.8	0	0	1	0.9	30
Meningitis	20	18.3	2	1.8	3	3.7	1	0.9	0	0	26
Septicaemia	32	29.4	8	7.3	12	11.0	1	0.9	0	0	53
Total	77	70.6	10	9.2	19	17.4	2	1.8	1	0.9	109

3.4.5 Sequelae and outcomes

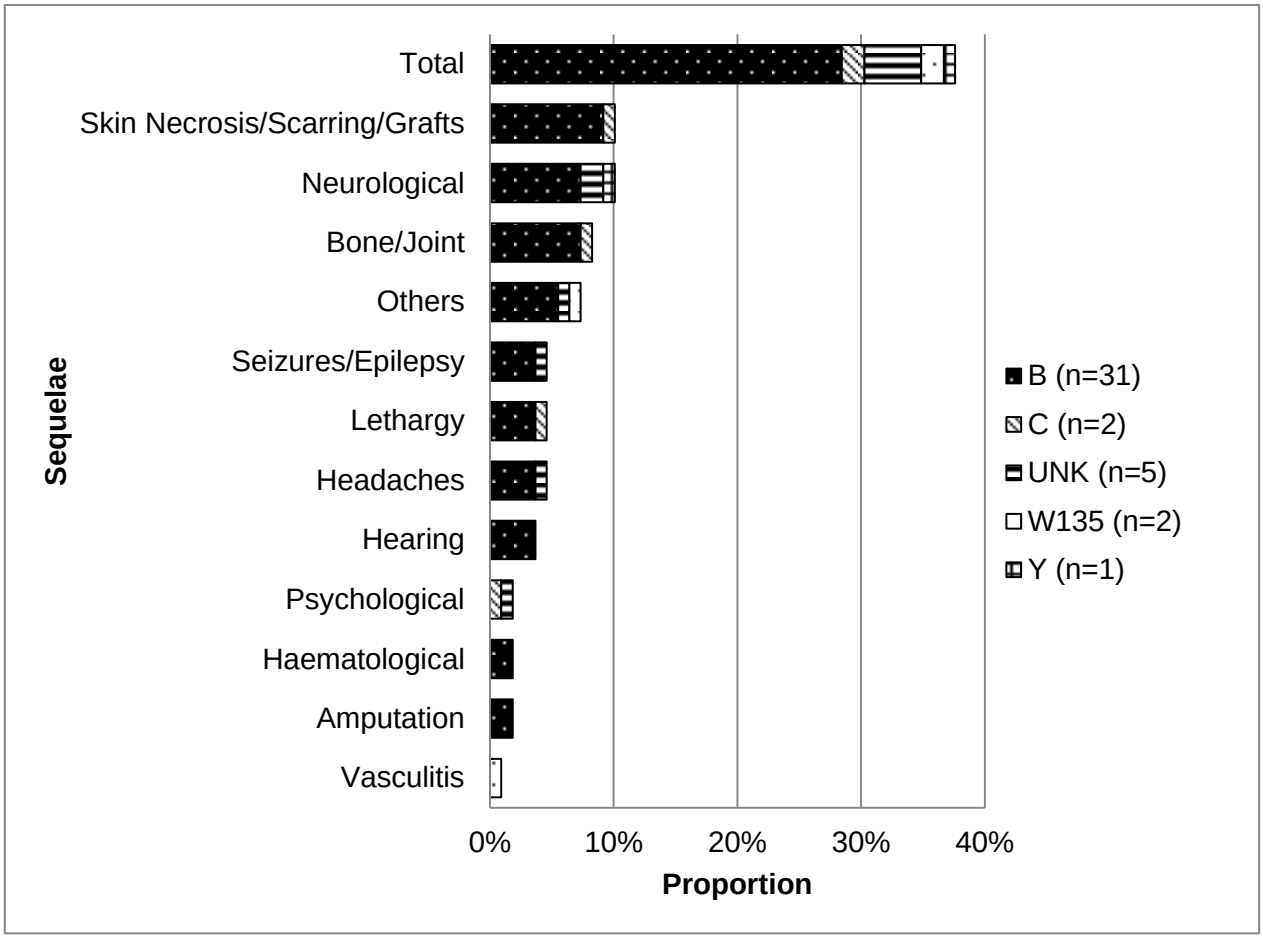
Over half of the patients (58.7%, n=64) recovered without sequelae. Sequelae occurred in 37.6% (n=41) of 109 IMD patients. A higher proportion of children with serogroup B disease developed sequelae (41.3% (31/75)) than those with serogroup C disease, 22.2% (2/9), although this was not statistically significant (p=0.280) (Figure 4).

Figure 4: Outcomes of IMD patients



For two cases, outcome was unknown, as children were transferred back to a rural hospital to complete their treatment and were lost to follow up. Inpatient death occurred in two patients, both with meningococcal septicaemia. One patient was a 15½ year old Caucasian male who presented to an Adelaide metropolitan hospital with serogroup B disease prior to transferring to the WCH and died approximately three hours later. The second was an 11 month old Aboriginal female who was admitted to a rural hospital with serogroup C disease, prior to transferring to the WCH on day two and died on day 16. The most commonly observed sequelae were skin necrosis/scarring, neurological problems and bone/joint conditions (Figure 5).

Figure 5: Percentage of patients with each type of sequelae



Minor sequelae such as chronic lethargy or headaches were reported in 4.5% of IMD children (Table 3).

Table 3: Number and percentage of patients with major and minor sequelae

Sequelae	n (%)	Serogroup n (%)				
		B	C	Unknown	W135	Y
Major[#]						
Amputation	2 (1.8%)	2 (1.8%)	0	0	0	0
Skin Necrosis/Scarring/ Grafts	11 (10.1%)	10 (9.2%)	1 (0.9%)	0	0	0
Seizures/Epilepsy	5 (4.5%)	4 (3.7%)	0	1 (0.9%)	0	0
Bone/Joints	9 (8.2%)	8 (7.3%)	1 (0.9%)	0	0	0
Neurological	11 (10.1%)	8 (7.3%)	0	2 (1.8%)	0	1 (0.9%)
Psychological	2 (1.8%)	0	1 (0.9%)	1 (0.9%)	0	0
Hearing loss	4 (3.7%)	4 (3.7%)	0	0	0	0
Vasculitis	1 (0.9%)	0	0	0	1 (0.9%)	0
Haematological	2 (1.8%)	2 (1.8%)	0	0	0	0
Minor						
Headaches - chronic	5 (4.5%)	4 (3.7%)	0	1 (0.9%)	0	0
Lethargy - chronic	5 (4.5%)	4 (3.7%)	1 (0.9%)	0	0	0
Others*	8 (7.3%)	6 (5.5%)	0	1 (0.9%)	1 (0.9%)	0

Major sequelae included limb amputation, skin necrosis/scarring, seizures, bone/joint problems (bone deformities, reactive arthritis and knee pain), neurological (hydrocephalus, cerebral infarct, developmental delay), psychological (autism and post-traumatic stress disorder) and haematological (anaemia and thrombocytosis).

* Others include unconfirmed hearing loss (n=2), unconfirmed development delay (n=1), unconfirmed neurological impairment (n=1) and cognitive development delay (n=1), possible attention deficit hyperactivity disorder (n=1), low body weight and poor growth (n=1) and tinnitus (n=1).

The duration of resolution of sequelae varied from 9 to 1 442 days with a median of 47 days (Supplementary Table 1).

Supplementary Table 1: Sequelae outcome list

Patient No.	Sequelae	Start Date	Resolution Date	Duration (Days)
1	Radiculopathy	Final outcome is unknown (followed up at a rural hospital)		
2	Unilateral Hearing Loss	Unresolved		
3	Optic Disc Swelling	Final outcome is unknown (followed up at a rural hospital)		
4	Headaches	7/02/2002	15/04/2002	67
5	Skin Necrosis	12/09/2001	UNK	
	Headaches	30/10/2001	UNK	
	Lethargy	30/10/2001	UNK	
	Articulation Problem	30/10/2001	UNK	
	Gross Motor Difficulties	30/10/2001	UNK	
6	Possible Development Delay	Unresolved		
7	Unilateral Hearing Loss	Unresolved		
8	Lethargy	UNK	UNK	
9	Seizures	13/05/2002	UNK	
10	Possible Hearing Loss	20/03/2002	UNK	
11	Unilateral Hearing Loss	Unresolved		
	Subdural Empyema	31/05/2005	7/07/2005	37
12	Esotropia	19/10/2003	27/06/2005	617
13	Possible Neurological Impairment	Final outcome is unknown (followed up at a peripheral hospital)		
	Septic Arthritis	25/08/2005	UNK	
14	Seizures	20/01/2004	UNK	
	Anaemia	16/01/2004	16/02/2004	31
	Thrombocytosis	21/01/2004	16/02/2004	26
15	Skin Necrosis/Grafts	20/04/2004	24/02/2005	310
	Skin scarring	24/02/2005	5/02/2009	1442
	Limb Deformities	Unresolved		
	Epilepsy	Unresolved		
16	Bilateral Cranial Nerve VI palsy	Unresolved		
	Right Cranial Nerve VII palsy	28/12/2005	UNK	
	Optic Disc Swelling	30/12/2005	24/02/2006	56
	Possible Attention Deficit Hyperactivity Disorder	29/11/2007	UNK	
17	Seizures	10/06/2007	UNK	
	Hydrocephalus (with Ventriculoperitoneal Shunt)	Unresolved		
	Non-specific Behavioural Problems	Unresolved		
18	Headache	21/08/2007	6/09/2007	16
	Tinnitus	28/08/2007	6/09/2007	9
19	Lethargy	2/02/2009	UNK	
	Knee Pain	28/01/2009	UNK	
20	Skin Necrosis /Grafts	23/12/2009	4/03/2010	71
	Skin scarring	Unresolved (compression garments required)		
21	Septic Arthritis	13/03/2010	7/04/2010	25
22	Headaches	23/04/2010	UNK	
	Lethargy	28/04/2010	UNK	

Patient No.	Sequelae	Start Date	Resolution Date	Duration (Days)
23	Headaches	23/07/2010	UNK	
	Seizure	11/07/2011	UNK	
24	Inflammatory Arthritis	5/07/2002	UNK	
25	Amputation	13/03/2003	UNK	
	Skin Necrosis/Grafts	13/02/2003	UNK	
26	Reactive Arthritis	24/04/2004	13/05/2004	19
27	Low Body Weight and Stature	Unresolved		
	Delayed Speech and Language Skills	13/03/2009	UNK	
	Anaemia	10/12/2006	16/04/2009	858
28	Unilateral Hearing Loss	Unresolved		
29	Skin Necrosis	30/04/2011	UNK	
30	Arthritis	8/07/2000	UNK	
31	Possible Cognitive Development Delay	Lost to follow up		
	Skin Necrosis/Grafts	13/08/2002	12/09/2002	30
32	Amputation Skin Necrosis/Scarring/Grafts Multiple Brain Infarct Visual Impairment Development Delay Possible Unilateral Hearing Loss	Final outcome is unknown (followed up at an interstate hospital)		
33	Speech Delay and Articulation Problems	28/10/2010	UNK	
34	Skin Necrosis/Grafts	15/06/2003	UNK	
35	Vasculitis	10/08/2008	UNK	
36	Skin Necrosis/Grafts	16/04/2009	UNK	
37	Skin Necrosis/Grafts	21/08/2006	30/11/2006	101
38	Global Developmental Delay Autism	Unresolved		
39	Septic Arthritis	3/09/2003	30/09/2003	27
40	Reactive Arthritis	10/10/2005	UNK	
41	Lethargy	20/08/2000	10/10/2000	51
	Skin Keloid Scar	2/07/2001	UNK	
	Post-Traumatic Stress Disorder	15/03/2001	1/05/2001	47

Septicaemia with meningitis was associated with a higher risk of sequelae (67.9%, 19/28) than meningitis alone (30.8%, 8/26) (p=0.002) or septicaemia alone (27.4%, 14/51) (p<0.001). Children with sequelae were more likely to be managed in ICU/HDU (70.7%, 29/41) than those without sequelae (45.3%, 29/64) (p=0.012). Half (16/31) of infants less than one year of age experienced sequelae compared to 33.8% (25/74) of children aged one year or older (p=0.090). No reduction in

proportion of children with sequelae in the pre versus post MenC vaccine era was observed (27/66 vs 14/39, p=0.611).

Transferred children were more likely to require HDU/ICU management (72.2%, 39/54) compared to those who were not transferred (41.8%, 23/55) (p=0.002). The rate of sequelae was not significantly different between transferred children (46.0%, 23/50) and those who were admitted directly to the WCH (32.7%, 18/55) (p=0.165). Children transferred from a metropolitan hospital were, however, more likely to develop sequelae (60.0%, 12/20) than those who were transferred from a rural hospital (30.8%, 8/26) (p=0.051). Children who first presented to the emergency department of the WCH had a lower sequelae rate (22.6%, 7/31) than children who first presented to the emergency department of other hospitals prior to admission to the WCH (47.2%, 17/36) (p=0.039). The rate of sequelae (44.7%, 17/38) for children who were seen by their family physician first, was higher than those who presented directly to the emergency department of the WCH (22.6%, p=0.058), and was similar to children who presented to the emergency department of other hospitals (47.2%, p=0.830).

Prematurity (n=8) was one of the most frequent past medical histories identified in children with IMD. For children aged less than one year, sequelae occurred in all infants with a history of prematurity (100%, 4/4) and admission ages ranging from 4 to 10 months, compared to full-term infants (44.4%, 12/27) (χ^2 1df=4.306, P=0.038).

Follow-up for those with sequelae varied from zero to 3 655 days (median: 173 days) with three patients followed up at their local hospital (Supplementary Digital Table 1). The median number of outpatient appointments attended by patients following discharge was three (range: 0–65 appointments).

3.4.6 Predictors of development of sequelae

Diagnosis type, temperature ≥ 39°C at admission and parenteral antibiotics given prior to admission were independent predictors of development of sequelae (Table 4). Children diagnosed with meningitis and septicaemia were more likely to develop sequelae than those diagnosed with septicaemia (OR: 15.48; p<0.001) or meningitis alone (OR: 7.83; p=0.002). Children with a high temperature at presentation had a 4.5 times higher risk of developing sequelae than those whose body temperature was < 39°C (p=0.012). Unexpectedly, compared with children who received their first parenteral antibiotics in the hospital setting, parenteral antibiotics administered at the family physician clinic prior to admission was a risk factor (OR: 11.97; p=0.007) for development of sequelae (Table 4). Nine of ten patients who received parenteral antibiotics at the family physician clinic were given penicillin. Conversely, the majority of patients who presented to a hospital (77.6%, 76/98) received ceftriaxone. The children who were treated with parenteral antibiotics at the family physician clinic, presented with severe IMD symptoms such as rash (80%, 8/10), fever (100%, 10/10), seizure (20%, 2/10), irritability (30%, 3/10) or confusion (20%, 2/10), and most (90%, 9/10) required ICU and/or HDU management during hospitalisation.

Table 4: Risk factors associated with sequelae

Univariate Associations								**Multivariate Logistic Regression Analysis**			
Variables	Patients with Sequelae		Patients without Sequelae		Odds Ratio	95% Confidence Interval (CI)	p-value	Risk Factors	Odds Ratio	95% Confidence Interval (CI)	p-value
Fever: body temperature ≥ 39°C	n	%	n	%				**Fever: body temperature ≥ 39°C**			
Missing	2	66.7	1	33.3					-	-	-
No	27	34.2	52	65.8	1.00	-			-	-	-
Yes	12	52.2	11	47.8	2.10	0.82-5.38	0.122	Body temperature ≥ 39°C vs body temperature < 39°C	4.45	1.39-14.24	0.012
Early Antibiotic Treatment	n	%	n	%				**Early Antibiotic Treatment**			
Missing	0	0	1	100.0				-	-	-	-
No	35	36.5	61	63.5	1.00	-		-	-	-	-
Yes	7	77.8	2	22.2	6.28	1.23-31.94	0.027	Antibiotics administered at the family physician clinic vs antibiotics NOT administered prior to admission	11.97	2.00-71.59	0.007
Diagnosis Types	n	%	n	%			0.002[a]	**Diagnosis types**			<0.001[a]
Septicaemia	14	27.5	37	72.5	1.00	-		Meningitis and Septicaemia vs Septicaemia alone	15.48	4.41-54.37	<0.001
Meningitis	8	30.8	18	69.2	1.18	0.42-3.31	0.761	Meningitis vs Septicaemia	1.97	0.60-6.54	0.264
Meningitis and Septicaemia	19	67.9	9	32.1	5.58	2.05-15.22	0.001	Meningitis and Septicaemia vs Meningitis alone	7.83	2.17-28.28	0.002
Prematurity[#]	n	%	n	%							
No	36	37.1	61	62.9	1.00	-		-	-	-	-
Yes	5	62.5	3	37.5	2.82	0.64-12.52	0.172	-	-	-	-
Hypotension[#]	n	%	n	%							
No	24	35.3	44	64.7	1.00	-		-	-	-	-
Yes	15	55.6	12	44.4	2.29	0.92-5.68	0.073	-	-	-	-

The prematurity and hypotension were not included in the multivariate logistic regression model due to non-significance.

Univariate Logistic Regression Analysis								Multivariate Logistic Regression Analysis			
Variables	Patients with Sequelae		Patients without Sequelae		Odds Ratio	95% Confidence Interval (CI)	p-value	Risk Factors	Odds Ratio	95% Confidence Interval (CI)	p-value
Age	Mean	(95% CI)	Mean	(95% CI)							
	3.68	(2.13-5.24)	3.86	(2.81-4.91)	0.99	0.91-1.08	0.843	-	-	-	-
Gender	n	%	n	%							
Female	20	35.7	36	64.3	1.00	-		-	-	-	-
Male	21	42.9	28	57.1	1.35	0.62-2.97	0.455	-	-	-	-
Indigenous Status	n	%	n	%							
Missing	1	50.0	1	50.0				-	-	-	-
Non-Indigenous	37	39.8	56	60.2	1.00	-		-	-	-	-
Indigenous	3	30.0	7	70.0	0.65	0.16-2.67	0.549	-	-	-	-
Area of Residence	n	%	n	%							
Highly Access/Access	36	39.1	56	60.9	1.00	-		-	-	-	-
Mod Access/Remote	5	38.5	8	61.5	0.97	0.30-3.21	0.963	-	-	-	-
Socio-Economic Indexes for Areas (SEIFA)	n	%	n	%			1.000[b]				
High (67th – 100th percentile)	7	38.9	11	61.1	1.00	-		-	-	-	-
Medium (34th – 66th percentile)	13	39.4	20	60.6	1.02	0.32-3.32	0.972	-	-	-	-
Low (1st – 33rd percentile)	21	38.9	33	61.1	1.00	0.34-2.99	1.000	-	-	-	-
Respiratory Past Medical History	n	%	n	%							
N	37	38.9	58	61.1	1.00	-		-	-	-	-
Y	4	40.0	6	60.0	1.05	0.28-3.95	0.948	-	-	-	-
Serogroup	n	%	n	%							
Missing	5	27.8	13	72.2				-	-	-	-
Serogroup non-B (A, C, W135)	5	41.7	7	58.3	1.00	-		-	-	-	-
Serogroup B	31	41.3	44	58.7	0.99	0.29-3.40	0.983	-	-	-	-

[a]The p-value assesses the overall association between Diagnosis Type and the development of sequelae.

[b]The p-value assesses the overall association between SEIFA and the development of sequelae.

3.5 DISCUSSION

To our knowledge, no studies have analysed clinical characteristics, serogroup data and clinical outcomes in Australian children since Hansman reported the serogroup and epidemiology of meningococcal disease between 1971 and 1980.[16] The seasonal pattern of IMD identified in our study is consistent with national surveillance data.[17] The majority of cases in our study were associated with serogroup B, with a high rate (37.6%) of sequelae, consistent with prior studies in the United States and England.[18-20] However, a lower sequelae rate of 9–19% has been observed in the literature.[5, 21, 22] Since the WCH is a tertiary paediatric institution, severe cases are more likely to be transferred or referred to the WCH which may lead to bias and a higher sequelae rate than those previously reported in other studies. The risk of developing complications or sequelae is often highest in the very young compared to older children and adults [23] and our study supported this finding with 50% of infants less than one year of age developing sequelae. History of prematurity was significantly associated with an increased sequelae rate in IMD infants less than one year of age. This finding is of clinical importance and has not previously been identified in the literature; however the number of premature infants within this study remains small and this finding warrants further investigation. Neuro-developmental impairment was one of the most common sequelae identified in this study and is likely to have the most profound impact on children and their families. A recently published UK study found children with IMD were more likely to have deficits in executive function and multiple aspects of memory.[20] In addition, chronic lethargy and headaches were reported by children in this study and similarly high levels of mental fatigue were noted in Norwegian and UK studies.[24, 25] Septicaemia with meningitis was

associated with more severe disease and an increased risk of sequelae, which is consistent with the findings of a study in Canada.[5] Sequelae occurred more frequently following serogroup B than serogroup C disease, which is different to the findings in other studies.[5, 12, 20, 26] but the difference was not significant possibly due to the small sample size. This finding may differ from studies in other countries due to difference in circulating meningococcal subtypes. Transfer from another hospital for treatment was associated with an increased risk of requirement for ICU management. These findings were also observed in a study in Western Australia.[21] It may indicate that patients transferred from peripheral hospitals have more severe disease requiring intensive treatment in a tertiary paediatric hospital, or alternatively to a less rapid diagnosis and onset of treatment. Early antibiotic treatment, namely parenteral antibiotic administration prior to admission, was identified as an unexpected risk factor of developing sequelae. This result should be interpreted with caution due to the small number of children who received antibiotic treatment prior to admission (n=10). It is arguable that the severity of disease may account for poor outcomes, as these children presented to the family physician with severe IMD symptoms including rash, seizure, or irritability with most requiring ICU and/or HDU management. A systematic review showing the conflicting results of the effects of early antibiotic treatment in studies in Denmark, UK and New Zealand, suggests confounding factors and the proportions of cases treated could explain the heterogeneity in findings between studies.[27] No studies have previously identified that a body temperature higher than or equal to 39°C was a strong predictor of development of sequelae. This finding may be helpful for triage nurses and clinicians to prioritise patient assessment, management and follow-up. Our study revealed IMD admissions

required a wide variety of healthcare resources e.g. speech pathology, social work and aboriginal liaison officer assistance. Aboriginal children admitted with IMD were over represented and previous studies have identified aboriginal children are at increased risk of hospitalised IMD.[28, 29]

Two cases of serogroup C infection occurred in previously vaccinated children. Vaccine failures may be due to waning immunity, host factors or problems in storage or administration of the vaccine.[11] Several countries (UK, USA) have implemented an adolescent MenC/MenACWY booster program to avoid the potential for vaccine failure following reduction in antibody titres after 3-5 years.[30]

Our study has the limitations of a retrospective audit study including imperfect hospital records, and incomplete data due to loss to follow-up. In addition, the psychological impact on a child's life is difficult to evaluate through hospital note review.

Since serogroup B disease dominated this study population, our findings may help to inform future decisions about inclusion of MenB vaccines in paediatric immunisation programs to reduce the devastation to children and their families from this life-threatening infection and its consequences.

3.6 REFERENCES

1. Hart CA, Thomson AP. Meningococcal disease and its management in children. *BMJ.* 2006 Sep 30;333(7570):685-90.

2. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine*. 2009 Jun 24;27 Suppl 2:B51-63.

3. Trotter CL, Chandra M, Cano R, et al. A surveillance network for meningococcal disease in Europe. *FEMS Microbiology Reviews.* 2007 Jan;31(1):27-36.

4. Bilukha OO, Rosenstein N. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and Reports*. 2005 May;54(RR-7):1-21.

5. Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec, Canada, 1990-1994. *Clin Infect Dis*. 1998 May;26(5):1159-64.

6. Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J*. 1996 Nov;15(11):967-78; quiz 79.

7. Number of notifications of Meningococcal disease (invasive), Australia, in the period of 1991 to 2011 and year-to-date notifications for 2012. [Department of Health and Ageing web site]. August 2012. Available from: http://www9.health.gov.au/cda/Source/Rpt_3.cfm. Accessed 15 August, 2012.

8. Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2011. *Commun Dis Intell.* 2012 Sep;36(3):E251-62.

9. Annual report of the Australian Meningococcal Surveillance Programme, 2009. *Commun Dis Intell.* 2010 Sep;34(3):291-302.

10. Australian Meningococcal Surveillance Programme annual report, 2010. *Commun Dis Intell.* 2011 Sep;35(3):217-28.

11. *Guidelines for the early clinical and public health management of meningococcal disease in Australia* 2007, Communicable Diseases Network Australia, Department of Health and Ageing, Canberra.

12. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R. The Disease Burden of Invasive Meningococcal Serogroup B Disease in Canada. *Pediatr Infect Dis J*. 2013 Jan;32(1):e20-e25.

13. Hosmer DW, Lemeshow S: *Applied Logistic Regression.* 2nd ed. New York: Wiley; 2000.

14. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005 Jan;6(1):2-8.

15. Goldstein B, Giroir B, Randolph A. Reply: Values for Systolic Blood Pressure. *Pediatr Crit Care Med*. 2005;6(4):500-1.

16. Hansman D. Meningococcal disease in South Australia: incidence and serogroup distribution 1971-1980. *J Hyg (Lond).* 1983 Feb;90(1):49-54.

17. Jelfs J, Munro R. Epidemiology of meningococcal disease in Australia. *J Paediatr Child Health.* 2001 Oct;37(5):S3-6.

18. Karve S, Misurski D, Miller J, Davis KL. Costs of Sequelae Associated with Invasive Meningococcal Disease: Findings from a US Managed Care Population. *Health Outcomes Research in Medicine.* 2011;2(4):e215-e26.

19. Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. *Human Vaccines.* 2011 Apr;7(4):458-65.

20. Viner RM, Booy R, Johnson H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. *Lancet Neurol.* 2012 Sep;11(9):774-83.

21. Olesch CA, Knight GJ. Invasive meningococcal infection in Western Australia. *J Paediatr Child Health.* 1999 Feb;35(1):42-8.

22. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2010 May;10(5):317-28.

23. Jones D. Epidemiology of meningococcal disease in Europe and the USA. In: Cartwright K, editor. *Meningococcal disease.* Chichester: John Wiley & Sons; 1995. p. 147-57.

24. Sander J, Bay D, Gedde-Dahl TW, et al. Late sequelae after meningococcal disease. A controlled study in young men. *NIPH Ann.* 1984 Jun;7(1):3-11.

25. Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. *Pediatrics*. 2009 Mar;123(3):e502-9.

26. Pace D, Pollard AJ. Meningococcal disease: clinical presentation and sequelae. *Vaccine.* 2012 May;30 Suppl 2:B3-9.

27. Hahne SJ, Charlett A, Purcell B, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ.* 2006 Jun;332(7553):1299-303.

28. Massey P, Durrheim D. Aboriginal and Torres Strait Islander peoples at higher risk of invasive meningococcal disease in NSW. *New South Wales Public Health Bulletin.* 2008;19(6):100-3.

29. Hanna J, McCall B, Murphy D. Invasive meningococcal disease in north Queensland, 1990-1994. *Commun Dis Intell.* 1996;20:320-4.

30. Booy R, Richmond P, Nolan T, et al. Three-year antibody persistence and safety after a single dose of combined haemophilus influenzae type b (Hib)-Neisseria meningitidis serogroup C-tetanus toxoid conjugate vaccine in Hib-primed toddlers. *Pediatr Infect Dis J.* 2013;32(2):169-74.

This paper has provided valuable and detailed information regarding long-term outcomes of sequelae, clinical and socio-demographic factors associated with development of sequelae, and hospital resources required for the clinical management of acute IMD infection and sequelae. Due to the rarity of the disease, our sample size is small and further national studies would be warranted.

CHAPTER 4: INPATIENT COSTS AND HEALTH SERVICE USE ASSOCIATED WITH IMD IN AUSTRALIAN CHILDREN

The article, “The economic burden of invasive meningococcal disease in Australian children’, investigated inpatient costs and hospital services used during acute admissions for all children and during the periods of IMD related readmissions for children who developed sequelae. The article was submitted to Journal “Vaccine” and is currently under review.

As previous research data were not stratified by serogroup due to lack of serotype data, the impact of meningococcal serogroup B disease has not been assessed, revealing a knowledge gap about healthcare resource consumption and the need for costing studies to assist with determining the policy implications of a new meningococcal B vaccination program. We identified the research gap and thereby addressed research questions by evaluating the inpatient costs and outpatient service use by serogroup as well as age, gender, diagnosis type, previous medical diagnosis and sequelae.

Our study results show presence of sequelae, serogroup B infection, infants aged less than one year and male gender, were significantly associated with higher inpatient costs and LOS ($p<0.001$) (see Figures 1 and 2).

Figure 1: Mean predicted inpatient costs (2011 Australian dollars) during acute admissions

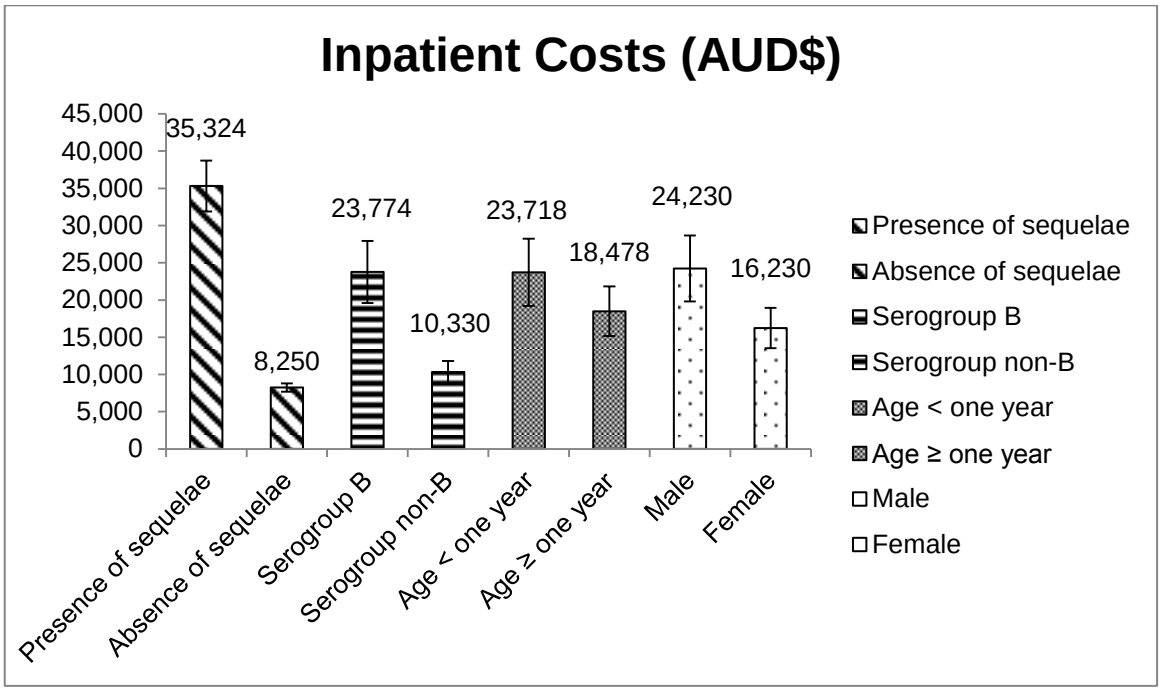
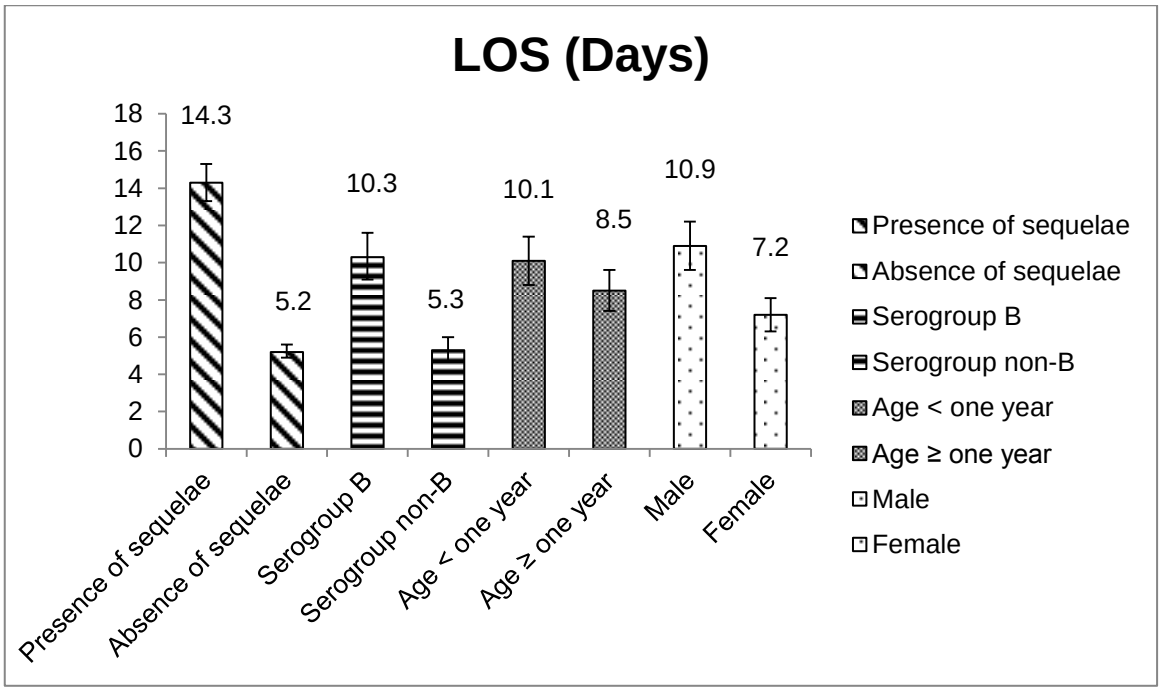


Figure 2: Mean predicted LOS during acute admissions



TITLE:

The economic burden of invasive meningococcal disease in Australian children

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NOTE:
Statements of authorship appear on page 106 in the print copy of the thesis held in the University of Adelaide Library.

4.1 ABSTRACT

Background: Invasive meningococcal disease (IMD) remains a serious public health concern due to a sustained high case fatality rate and morbidity in survivors. This study aimed to estimate the hospital service costs associated with IMD and variables associated with the highest costs in Australian children admitted to a tertiary paediatric hospital.

Methods: Clinical details were obtained from medical records and associated inpatient costs were collected and inflated to 2011 Australian dollars using the medical and hospital services component of the Australian Consumer Price Index. Both unadjusted and adjusted analyses were undertaken. Multivariate regression models were used to adjust for potential covariates and determine independent predictors of high costs and increased length of hospital stay.

Results: Of 109 children hospitalised with IMD between May 2000 – April 2011, the majority were caused by serogroup B (70.6%). Presence of sequelae, serogroup B infection, male gender, infants less than one year of age, and previous medical diagnosis were associated with higher inpatient costs and length of stay (LOS) in hospital ($p<0.001$) during the acute admission. Children diagnosed with septicaemia had a longer predicted LOS ($p=0.033$) during the acute admission compared to those diagnosed with meningitis alone or meningitis with septicaemia. Serogroup B cases incurred a significantly higher risk of IMD related readmissions (IRR: 21.1, $p=0.008$) for patients with sequelae. Serogroup B infection, male gender, diagnosis of septicaemia, infants less than one year of age,

and no previous medical diagnosis were more likely to have higher inpatient costs and LOS during the IMD related readmissions for patients with sequelae ($p<0.05$).

Conclusion: Although IMD is uncommon, the disease severity and associated long-term sequelae result in high health care costs, which should be considered in Meningococcal B vaccine funding considerations.

4.2 INTRODUCTION

Neisseria meningitidis, is responsible for causing invasive meningococcal disease (IMD), a serious bacterial infection worldwide.[1-4] Six of thirteen *N. meningitidis* subgroups (A, B, C, W_{135}, X and Y) cause clinical disease.[5-7] Despite advanced antibiotic therapy, meningococcal disease remains a serious public health concern due to a sustained high case fatality rate of 5-15% with up to 57% of survivors developing sequelae.[8-12] Whilst meningococcal disease affects all age groups, surveillance data show a bimodal age distribution with the highest rates in the 0 to 4 year age group and a second peak in the 15 to 24 year age group.[13] Children aged less than five years have the highest incidence rate in Australia (average annual age-specific rate: 4.8 per 100,000 population).[14] IMD is more commonly reported in infants less than one year of age worldwide.[5, 6, 15, 16]

Since the implementation of the national meningococcal C (MenC) vaccination program in 2003 in Australia, the number of notifications of IMD has declined from 687 in 2002 to 241 in 2011.[14] Serogroup B now predominates in Australia, with the proportion of laboratory-confirmed cases increasing 21%, from 63% in 2002 to 84% in 2011.[17, 18] A meningococcal B (MenB) vaccine (4CMenB vaccine, Bexsero®) has recently been licensed in Australia. However, the Joint Committee on Vaccination and Immunisation (JCVI) in the UK did not recommend introduction of Bexsero® vaccine into the routine immunisation schedule based on results of cost-effectiveness analyses.[19] Bexsero® was determined to be not cost-effective by the JCVI and has not yet been implemented in any publicly funded national immunisation programs.

A number of studies estimating the costs of meningococcal disease were previously conducted in the US.[9, 11, 20-22] All these studies used ICD diagnosis codes which were not verified against laboratory results or hospital records. This may lead to underestimation or overestimation of costs due to coding errors as acknowledged by the authors. The lifelong costs of treatment of acute meningococcal infection and management of long-term sequelae were estimated in a UK study by developing two severe scenarios of meningitis and septicaemia based on systematic reviews of the literature, interviews with IMD survivors and their families, and discussion with clinicians.[23] However, these were estimated costs rather than actual costs which relied on assumptions of resources used by survivors. As previous research data were not stratified by serogroup due to lack of serotype data, the economic impact of meningococcal B disease has not adequately been assessed.

Costing studies are required to estimate the cost saving and the medical benefits to inform public funding decisions such as immunisation programs.[24] A number of previous cost-effectiveness studies of meningococcal vaccination programs paid little attention to key drivers of economic evaluations including length of stay in hospital, proportion and length of stay in High Dependence Units (HDU) or Intensive Care Units (ICU), proportion of survivors with long-term sequelae, and long-term costs associated with sequelae following IMD.[25-30] A recent economic evaluation study assessing MenB vaccination, has acknowledged the paucity of such data.[31] It has been recognised that the potential benefits of the meningococcal vaccination program could be underestimated if the additional costs of managing long-term sequelae were overlooked.[32]

Costs associated with inpatient services are a major component of health care utilisation in the management of IMD [9, 11, 21] and are important in estimating the overall direct cost burden of IMD. Our study aimed to estimate costs associated with IMD hospitalisation and sequelae in children and determine factors (e.g. serogroup, age and gender) significantly associated with high costs for future economic evaluation of new meningococcal vaccination programs.

4.3 METHODS

4.3.1 Study design and population

This study was conducted at a tertiary paediatric hospital in Adelaide, South Australia. The IMD cases were identified as per definitions previously reported.[33] Patients who developed sequelae, were followed from 5 to 3659 days (mean [95% CI]: 645.8 [403.3 to 939.3]) during the period from the acute admission day to the day of their last IMD related outpatient visit OR to the discharge day of the acute inpatient admission if patients were not followed up at the tertiary paediatric hospital. For those without sequelae, the observation period was the length of hospital stay during the acute admission, which varied from 1 to 19 days (mean [95% CI]: 5.3 [4.7 to 6.0]).

Clinical data on IMD hospitalisation in children aged <18 years between May 2000 and April 2011 were collected. Both laboratory-confirmed and probable (clinician diagnosis, unconfirmed laboratory diagnosis) cases were included in the study. Probable cases and laboratory-confirmed cases with serotypes C, W_{135}, Y and unknown were categorised as serogroup non-B disease. Clinical data such as patient characteristics and clinical outcomes were extracted from hospital and outpatient records. Direct medical costs were extracted from the hospital Health Informatics, Performance, Planning and Outcomes Unit, and included costs of medical ward, pathology, imaging, allied health (e.g. physiotherapy and speech pathology), pharmacy, use of theatre suite, the paediatric intensive care unit, prosthesis, medical and surgical supplies, hotel services, direct goods and services and overheads (those that do not provide services/care directly to patients, are allocated to direct patient areas as overhead costs i.e. finance,

human resource, cleaning, etc.). In addition to acute admission costs, inpatient costs during the IMD related readmissions at this tertiary paediatric hospital were obtained for patients who developed sequelae. Older values were inflated to 2011 Australian dollars using the medical and hospital services component of the Australian Consumer Price Index.[34]

4.3.2 Outcome measures

Outcome measures were the length of stay (LOS) in hospital during the acute admission and IMD related readmissions. Outcome measures were estimated by serogroup, age, gender, diagnosis type, absence or presence of a previous medical diagnosis and/or absence or presence of sequelae. The number of IMD related outpatient visits and frequency of IMD related readmissions following the primary admission were outcome measures and reported as incidence rate ratios (IRR) for patients with sequelae.

4.3.3 Cost measures

Cost measures included inpatient costs during the acute admission and readmissions associated with IMD. Cost measures were assessed in relation to serogroup, age, gender, diagnosis type, absence or presence of a previous medical diagnosis and/or absence or presence of sequelae.

4.3.4 Statistical analysis

Data were analysed using Stata, version 11 (StataCorp). Patient characteristics were presented as mean values and standard deviations for continuous variables

and proportions for categorical variables. Appropriate statistical tests such as χ^2 tests and Student's t-tests were performed to assess differences in means and proportions by serogroup and absence or presence of sequelae.

Both unadjusted and adjusted analyses were undertaken. Due to the non-normal distribution of unadjusted cost and outcome data, mean values were reported with 95% confidence intervals (95% CI) derived from non-parametric bootstrap sampling.[35] The unadjusted mean values were statistically compared in each comparison group such as serogroup (B or non-B), age group (less than one year of age or equal and greater than one year of age), gender (male or female), diagnosis type (septicaemia, meningitis, or septicaemia with meningitis), previous medical diagnosis (presence or absence) and/or sequelae (presence or absence).

In adjusted analyses, multivariate regression models were used to adjust for potential covariates. We included the following variables as potential covariates in the multivariable analyses: serogroup (B or non-B), age group (less than one year or equal and greater than one year of age), gender (male or female), diagnosis type (septicaemia, meningitis, or septicaemia with meningitis), presence or absence of a previous medical diagnosis and/or presence or absence of sequelae. Sequelae were defined as any complications related to IMD that were not resolved at discharge following the acute admission or occurred following discharge after the acute admission.[36] The term 'previous medical diagnosis' referred to any medical condition recorded prior to the acute meningococcal admission, for example prematurity, asthma and bronchiolitis. Cases with missing data on the outcome or independent variables were not included in the analysis; for example

two inpatient deaths and two cases with unknown outcomes due to transferring back to a rural hospital were not included in the adjusted analyses.

The choice of regression models in the adjusted analyses was based on the nature of the cost and outcome measures. A generalised linear model (GLM) was used to analyse cost measures.[37, 38] Goodness of fit was determined using the modified Park test (for the GLM family) and the Pearson correlation test, the Pregibon link test, and the modified Hosmer and Lemeshow test (for the GLM link). For outcome measures such as LOS during the acute admission, characterised as non-zero count data, we used zero-truncated negative binomial regression models. With presence of zero day of readmission in patients with sequelae, negative binomial regression models were selected. Similarly, the increased or decreased use of hospital services for patients with sequelae, such as the number of outpatient visits and readmission frequencies, was assessed using the negative binomial regression models with adjustment of the covariates and follow-up duration and presented as IRR.

In addition to 12 confirmed C, Y or W_{135} cases, 12 laboratory confirmed cases with non-determined or non-groupable serogroup results and 6 clinically diagnosed cases with negative results on confirmatory meningococcal testing, were included in the serogroup non-B group. Since more than half of serogroup non-B cases had unknown serogroup, deterministic sensitivity analyses were performed to deal with parameter uncertainty. The deterministic sensitivity analysis, involves varying one or more parameter(s) simultaneously and calculating the output under various scenarios. In our study, the deterministic one-way sensitivity analyses were

undertaken to test the robustness of the adjusted findings. The following scenarios were considered to investigate if cases with unknown serogroup could affect the association between the adjusted inpatient costs and serogroup B:

1. Removing clinically diagnosed cases from analyses and including laboratory confirmed cases with unknown serogroup in the non-B group;
2. Including all cases with unknown serogroup in the B group;
3. Removing clinically diagnosed cases from analyses and including laboratory confirmed cases with unknown serogroup in the B group;
4. Removing all cases with unknown serogroup from analyses.

4.3.5 Ethics

The study was approved by the Women's and Children's Health Network Human Research Ethics Committee.

4.4 RESULTS

4.4.1 Patient characteristics

Patient characteristics are presented in Table 1. Of 109 eligible cases identified, 102 cases were laboratory confirmed by PCR, culture, IgM antibody or antigen tests. The majority were infected with serogroup B (70.6%, n=77) with 9.2% (n=10) caused by serogroup C, one case (0.9%) caused by serogroup Y and two cases (1.8%) caused by serogroup W_{135}. Serogroup was unknown for 12 laboratory confirmed cases (11.0%) with non-determined or non-groupable results. Seven (6.4%) cases were clinically diagnosed (probable) with no laboratory definitive or suggestive evidence. The non-B group included 13 serogroup C, Y or W_{135} patients, 12 laboratory confirmed patients with unknown serogroup, and 6 patients who were only clinically diagnosed. Since one probable case and one serogroup B case were lost to follow up due to being transferred back to a rural hospital and two inpatient deaths occurred in one serogroup B case and one serogroup C case, these four cases were not included in analyses. The details of clinical findings are reported elsewhere.[33]

Table 1: Patient characteristics in relation to sequelae and serogroup status

	Overall		Patients with sequelae		Patients without sequelae			Patients with serogroup B IMD		Patients with serogroup non-B IMD		
	n	%	n	%	n	%	p-value	n	%	n	%	p-value
All patients	109^	100	41	37.6	64	58.7		77	70.6	32	29.4	
Mean age (SD)	3.85 (4.53)		3.68 (4.92)		3.86 (4.19)		0.845	3.84 (4.87)		3.88 (3.66)		0.974
Admission age												
< one year	32	29.4	16	39.0	15	23.4	0.088	26	33.8	6	18.8	0.117
≥ one year	77	70.6	25	61.0	49	76.6		51	66.2	26	81.3	
Sex												
Female	59	54.1	20	48.8	36	56.3	0.454	40	51.9	19	59.4	0.479
Male	50	45.9	21	51.2	28	43.8		37	48.1	13	40.6	
Indigenous status												
Non-indigenous*	96	88.1	38	92.7	57	89.1	0.538	68	88.3	28	87.5	0.905
Indigenous	13	11.9	3	7.3	7	10.9		9	11.7	4	12.5	
Previous medical diagnosis												
Absent	73	67.0	26	63.4	45	70.3	0.461	53	68.8	20	62.5	0.522
Present	36	33.0	15	36.6	19	29.7		24	31.2	12	37.5	
Serogroup												
B	75	71.4	31	75.6	44	68.8	0.448	-	-	-	-	-
Non-B	30	28.6	10	24.4	20	31.2		-	-	-	-	
Diagnosis type												
Septicaemia	53	48.6	14	34.2	37	57.8	0.001	32	41.6	21	65.6	0.063
Meningitis	26	23.9	8	19.5	18	28.1		20	26.0	6	18.8	
Meningitis and septicaemia	30	27.5	19	46.3	9	14.1		25	32.5	5	15.6	
Transferred from other hospitals												
Not-transferred	55	50.5	18	43.9	37	57.8	0.164	34	44.2	21	65.6	0.041
Transferred	54	49.5	23	56.1	27	42.2		43	55.8	11	34.4	
Residential remoteness												
Moderately accessible/remote	15	13.8	5	12.2	8	12.5	0.963	13	16.9	2	6.3	0.142
Highly accessible/ accessible	94	86.2	36	87.8	56	87.5		64	83.1	30	93.8	
Socio-economic indexes for areas (SEIFA)												
High (67th – 100th percentile)	19	17.4	7	17.1	11	17.2	0.999	7	9.1	12	37.5	0.000
Medium (34th – 66th percentile)	34	31.2	13	31.7	20	31.3		23	29.9	11	34.4	
Low (1st – 33rd percentile)	56	51.4	21	51.2	33	51.6		47	61.0	9	28.1	
Initial medical presentation												
Family physicians	41	37.6	17	41.5	21	32.8	0.080	25	32.5	16	50.0	0.080
ED at other hospitals	37	34.0	17	41.5	19	29.7		31	40.3	6	18.8	
ED (at this tertiary paediatric hospital)	31	28.4	7	17.1	24	37.5		21	27.3	10	31.3	
ICU admission												
Hours of ICU stay (SD)	6.72 (9.02)		9.78 (10.51)		4.05 (6.80)		0.003	7.28 (9.22)		5.41 (8.51)		0.328
No admission to ICU	68	62.4	18	43.9	50	78.1	0.000	45	58.4	23	71.9	0.187
Admission to ICU	41	37.6	23	56.1	14	21.9		32	41.6	9	28.1	
HDU and ICU admission												
Hours of HDU/ICU stay (SD)	10.70 (11.70)		14.65 (13.26)		7.38 (9.53)		0.004	11.30 (12.04)		9.34 (10.93)		0.433
No admission to HDU/ICU	47	43.1	12	29.3	35	54.7	0.011	31	40.3	16	50.0	0.350
Admission to HDU/ICU	62	56.9	29	70.7	29	45.3		46	59.7	16	50.0	

^ Two inpatient deaths occurred and two children were transferred back to a rural hospital with unknown outcomes.

* Non-indigenous group includes two patients with unknown race.

Details of sequelae are shown in Table 2. Among 109 eligible patients, 37.6% (n=41) developed sequelae.

Table 2: Number and percentage of IMD patients with sequelae by serogroup

	Total		Serogroup B		Serogroup non-B	
Sequelae	**n**	**% of Patients with sequelae**	**n**	**% of Patients with sequelae**	**n**	**% of Patients with sequelae**
Total No. of patients with sequelae	**41**	**100.0**	**31**	**75.6**	**10**	**24.4**
Neurology	**11**	**26.8**	**8**	**19.5**	**3**	**7.3**
Radiculopathy	1	2.4	1	2.4	0	0.0
Subdural empyema	1	2.4	1	2.4	0	0.0
Bilateral cranial nerve VI palsy, right cranial nerve VII palsy and optic disc swelling	1	2.4	1	2.4	0	0.0
Hydrocephalus with ventriculoperitoneal shunt and non-specific behavioural problems	1	2.4	1	2.4	0	0.0
Multi cerebral infarct, visual impairment and developmental delay	1	2.4	1	2.4	0	0.0
Optic disc swelling	1	2.4	0	0.0	1	2.4
Esotropia	1	2.4	1	2.4	0	0.0
Articulation problem and gross motor difficulties	1	2.4	1	2.4	0	0.0
Delayed speech and language skills	1	2.4	1	2.4	0	0.0
Speech delay and articulation problems	1	2.4	0	0.0	1	2.4
Developmental delay	1	2.4	0	0.0	1	2.4
Skin Necrosis/Scarring/Grafts	**11**	**26.8**	**10**	**24.4**	**1**	**2.4**
Minor	**10**	**24.4**	**8**	**19.5**	**2**	**4.9**
Chronic headaches	5	12.2	4	9.8	1	2.4
Lethargy	5	12.2	4	9.8	1	2.4
Bone/Joint	**9**	**22.0**	**8**	**19.5**	**1**	**2.4**
Arthritis	7	17.1	6	14.6	1	2.4
Knee pain	1	2.4	1	2.4	0	0.0
Limb deformities	1	2.4	1	2.4	0	0.0
Others	**8**	**19.5**	**6**	**14.6**	**2**	**4.9**
Unconfirmed hearing impairment	2	4.9	1	2.4	1	2.4
Unconfirmed development delay	1	2.4	0	0.0	1	2.4
Unconfirmed neurological impairment	1	2.4	1	2.4	0	0.0
Unconfirmed cognitive development delay	1	2.4	1	2.4	0	0.0
Unconfirmed attention deficit hyperactivity disorder	1	2.4	1	2.4	0	0.0
Low body weight and stature	1	2.4	1	2.4	0	0.0
Tinnitus	1	2.4	1	2.4	0	0.0
Seizures/epilepsy	**5**	**12.2**	**4**	**9.8**	**1**	**2.4**
Hearing impairment	**4**	**9.8**	**4**	**9.8**	**0**	**0.0**
Amputation	**2**	**4.9**	**2**	**4.9**	**0**	**0.0**
Psychology	**2**	**4.9**	**0**	**0.0**	**2**	**4.9**
Autism	1	2.4	0	0.0	1	2.4
Post-traumatic stress disorder	1	2.4	0	0.0	1	2.4
Haematology	**2**	**4.9**	**2**	**4.9**	**0**	**0.0**
Anaemia	1	2.4	1	2.4	0	0.0
Anaemia and thrombocytosis	1	2.4	1	2.4	0	0.0
Vasculitis	**1**	**2.4**	**0**	**0.0**	**1**	**2.4**

4.4.2 Unadjusted analyses

The acute hospitalisation costs for the 109 identified IMD cases were estimated to be approximately AUD $2,325,908 (95% CI: $1,375,866 to $3,832,292; range: $915 to $461,493) with the cumulative hospital stay of 1,047 days (95% CI: 762 to 1,486). Overall, acute hospitalisation for patients with sequelae incurred almost six times higher inpatient costs ($p<0.001$) with a longer LOS ($p<0.001$) compared to those without sequelae. In comparison with IMD cases caused by non-B disease, the LOS ($p<0.001$) and inpatient costs ($p=0.039$) approximately doubled for serogroup B cases. Moreover, boys had a longer LOS than girls ($p=0.041$) (Table 3).

Table 3: LOS (days) and inpatient costs[$] per patient during ACUTE HOSPITALISATION by age group, serogroup, sequelae, diagnosis and previous medical diagnosis

			Unadjusted inpatient costs and LOS					Adjusted inpatient costs and LOS				
			n	Mean LOS (95% CI)	p-value	Mean costs (95% CI)	p-value	n	Mean LOS (95% CI)	p-value	Mean costs (95% CI)	p-value
Overall IMD	**n=109**	**All Patients**	**n=109**	9.6 (7.1 – 13.6)	-	21,338.6 (12,379.0 – 36,004.8)	-	**n=105[#]**	7.2 (6.1 – 8.4)	<0.001	12,311.5 (10,511.2 – 14,111.7)	<0.001
Sequelae	**n=105[#]**	**Presence**	**n=41**	16.5 (10.0 – 27.3)	<0.001	41,859.0 (19,498.1 – 78,818.0)	<0.001	**n=41**	14.3 (13.3 – 15.3)	<0.001	35,323.5 (31,908.1 – 38,738.8)	<0.001
		Absence	**n=64**	5.3 (4.7 – 6.0)		7,601.3 (6,547.9 – 8,726.3)		**n=64**	5.2 (4.9 – 5.6)		8,250.0 (7,687.9 – 8,812.2)	
Serogroup	**n=109**	**B**	**n=77**	11.3 (7.6 – 17.3)	<0.001	25,344.8 (13,342.8 – 47,156.0)	0.039	**n=75**	10.3 (9.1 – 11.6)	<0.001	23,774.1 (19,603.8 – 27,944.4)	<0.001
		Non-B	**n=32**	5.5 (4.6 – 7.0)		11,698.7 (7,480.0 – 19,493.9)		**n=30**	5.3 (4.7 – 6.0)		10,329.6 (8,834.0 – 11,825.2)	
Gender	**n=109**	**Male**	**n=50**	12.5 (7.2 – 21.0)	0.041	29,929.5 (11,633.3 – 61,072.9)	0.136	**n=49**	10.9 (9.6 – 12.2)	<0.001	24,230.0 (19,802.4 – 28,657.6)	<0.001
		Female	**n=59**	7.1 (5.7 – 9.4)		14,058.2 (9,668.9 – 20,620.0)		**n=56**	7.2 (6.3 – 8.1)		16,230.0 (13,511.5 – 18,948.5)	
Diagnosis type	**n=109**	**Septicaemia**	**n=53**	9.2 (5.5 – 16.8)	0.735	20,525.0 (9442.9 – 42,093.6)	0.557	**n=51**	9.8 (8.5 – 11.1)	0.033	19,300.4 (15,714.6 – 22,886.1)	0.115
		Meningitis	**n=26**	7.1 (5.7 – 10.1)		10,924.5 (8,722.3 – 14,042.5)		**n=26**	7.6 (6.6 – 8.6)		18,701.1 (15,252.4 – 22,149.7)	
		Meningitis & septicaemia	**n=30**	12.6 (8.1 – 22.5)		31,801.6 (13,108.0 – 7,3570.6)		**n=28**	9.2 (8.0 – 10.4)		24,076.2 (19,365.7– 28,786.8)	
Age	**n=109**	**< one year**	**n=32**	12.5 (7.8 – 21.6)	0.379	32,251.1 (13,576.1 – 71,429.4)	0.253	**n=31**	10.1 (8.8 – 11.4)	<0.001	23,717.7 (19,191.6 – 28,243.8)	<0.001
		≥ one year	**n=77**	8.4 (5.9 – 13.6)		16,803.6 (9,743.2 – 32,105.5)		**n=74**	8.5 (7.4 – 9.6)		18,478.4 (15,146.8 – 21,809.9)	
Previous medical diagnosis	**n=109**	**Presence**	**n=36**	11 (6.2 – 22.4)	0.650	24,576.4 (10,360.8 – 58,536.5)	0.717	**n=34**	9.5 (8.2 – 10.7)	<0.001	24,580.0 (19,821.7 – 29,338.2)	<0.001
		Absence	**n=73**	8.9 (6.5 – 12.7)		19,741.9 (11,234.0 – 37,485.2)		**n=71**	8.8 (7.6 – 10.0)		18,364.6 (15,032.1 – 21,697.0)	

$ All costs were inflated to 2011 Australian dollars using the medical and hospital services component of the Australian Consumer Price Index.

Two inpatient deaths and two cases with unknown outcomes were not included in analyses.

Cumulatively, AUD $465,579 was spent on 41 IMD related readmissions for 14 patients who developed sequelae. In patients with sequelae, serogroup B cases and infants aged less than one year had significantly higher inpatient costs ($p<0.001$ and $p=0.011$ respectively) and LOS ($p=0.002$ and $p=0.007$ respectively) during IMD related readmissions in comparison with non-B cases and children aged above one year. Surprisingly, patients with sequelae but no previous medical diagnosis incurred almost ten times higher readmission costs ($p=0.030$) with a longer readmission stay ($p=0.032$) compared to those with sequelae and a previous medical diagnosis (Table 4).

Table 4: LOS (days) and inpatient costs[$] per patient during IMD RELATED READMISSIONS by age group, serogroup, diagnosis and previous medical diagnosis in patients with sequelae only

				Unadjusted Inpatient Costs and LOS				Adjusted Inpatient Costs and LOS			
	n		n	Mean LOS (95% CI)	p-value	Mean costs (95% CI)	p-value	Mean LOS (95% CI)	p-value	Mean costs (95% CI)	p-value
All Patients with sequelae	**n=41**		**n=41**	4.8 (0.7 – 10.6)	-	11,355.6 (1,495.8 – 25,051.2)	-	1.1 (0.2 – 2.1)	0.021	1,342.5 (356.3 – 2,328.7)	0.008
Serogroup	**n=41**	**B**	**n=31**	6.2 (1.0 – 14.0)	0.002	14,901.7 (1,738.3 – 33,290.6)	<0.001	6.9 (4.0 – 9.8)	<0.001	14,124.2 (8,513.5 – 19,734.9)	<0.001
		Non-B	**n=10**	0.4 (0 – 0.8)		362.6 (0 – 881.2)		0.4 (0.3 – 0.6)		262.7 (202.7 – 322.7)	
Gender	**n=41**	**Male**	**n=21**	4.4 (0.3 – 15.2)	0.877	10,399.8 (757.1 – 36,507.1)	0.878	6.1 (3.1 – 9.0)	<0.001	14,114.4 (7,458.3 – 20,770.5)	<0.001
		Female	**n=20**	5.2 (0.4 – 13.0)		12,359.2 (487.5 – 30,810.9)		5.6 (2.8 – 8.3)		9,326.2 (5,060.8 – 13,591.6)	
Diagnosis type	**n=41**	**Septicaemia**	**n=14**	0.9 (0.1 – 2.1)	0.703	1,579.8 (175.8 – 4,267.2)	0.691	14.2 (8.0 – 20.4)	<0.001	26,437.2 (12,508.6 – 40,365.8)	0.024
		Meningitis	**n=8**	7.3 (0.4 – 27.3)		16,654.1 (616.1 – 48,311.5)		4.4 (2.4 – 6.3)		12,205.9 (6,219.2 – 18,192.6)	
		Meningitis & septicaemia	**n=19**	6.6 (0.3 – 17.5)		16,327.8 (451.1 – 42,189.5)		4.7 (2.6 – 6.7)		9,958.6 (5,165.7 – 14,751.6)	
Age	**n=41**	**< 1**	**n=16**	11.4 (0.9 – 24.8)	0.007	27,403.2 (7,402.6 – 61,782.0)	0.011	17.4 (12.8 – 22.1)	<0.001	36,474.8 (25,560.4 – 47,389.3)	<0.001
		≥ 1	**n=25**	0.6 (0.1 – 1.3)		1,085.1 (201.4 – 2,669.7)		0.4 (0.3 – 0.6)		951.3 (781.1 – 1,121.5)	
Previous medical diagnosis	**n=41**	**Presence**	**n=15**	0.8 (0.1 – 1.9)	0.032	1,637.1 (400.1 – 4,210.6)	0.030	5.1 (2.4 – 7.8)	<0.001	7,593.5 (3,987.8 – 11,199.3)	0.001
		Absence	**n=26**	7.1 (0.8 – 16.3)		16,962.4 (4,323.2 – 40,513.4)		6.9 (3.3 – 10.6)		18,806.7 (8,868.8 – 28,744.6)	

$ All costs were inflated to 2011 Australian dollars using the medical and hospital services component of the Australian Consumer Price Index.

4.4.3 Adjusted analyses

After adjusting for all potential covariates, predictors of higher inpatient costs and LOS during the acute admission included children aged less than one year, those infected with serogroup B disease, those who developed sequelae or had a previous medical diagnosis ($p<0.001$). Diagnoses of septicaemia alone and septicaemia with meningitis had a longer LOS than meningitis cases during the acute admission (Table 3). Serogroup B infection, male gender, diagnosis of septicaemia, infants aged less than one year, and absence of a previous medical diagnosis were associated with higher inpatient costs and LOS during the IMD related readmissions for patients with sequelae (Table 4). Results of sensitivity analyses indicate cases with unknown serogroup do not affect the direction of the association between high inpatient costs and serogroup B (Tables 5 and 6). Removal of cases with unknown serogroup from analyses or inclusion of these cases in the serogroup B group has little impact on the outcome.

For IMD patients with sequelae, the risk-adjusted rate of IMD-related readmissions was significantly higher for patients with serogroup B disease in comparison with non-B disease (IRR [95% CI]: 21.09 [2.23 to 199.63], $p=0.008$). Serogroup B cases had a 50% higher number of outpatient visits, compared to non-B serogroup cases, however the difference was not significant (IRR [95% CI]: 1.53 [0.82 to 2.85], $p=0.178$). Patients diagnosed with septicaemia alone had a significantly higher rate of IMD-related readmissions versus those with septicaemia and meningitis (IRR [95% CI]: 7.24 [1.29 to 40.45], $p=0.024$) or meningitis alone (IRR [95% CI]: 4.68 [0.70 to 31.49], $p=0.113$). Children with septicaemia were more likely to require outpatient services than those with septicaemia and meningitis

(IRR [95% CI]: 2.84 [1.23 to 6.56], p=0.014) or meningitis alone (IRR [95% CI]: 1.94 [0.95 to 3.98], p=0.069).

Table 5: One-way sensitivity analysis results of inpatient costs during ACUTE HOSPITALISATION

Scenario	Allocation		Adjusted Inpatient Costs		
	Laboratory confirmed cases with unknown serogroup (n=12)	Clinically diagnosed cases (n=6)	Serogroup	Mean costs 95% CI	p-value
Base case	Non-B	Non-B	B (n=75)	23,774.1 (19,603.8 – 27,944.4)	<0.001
			Non-B (n=30)	10,329.6 (8,834.0 – 11,825.2)	
1. Clinically diagnosed cases removed from analyses	Non-B	Missing data (excluded from analysis)	B (n=75)	23,651.6 (19,465.4 – 27,837.9)	<0.001
			Non-B (n=24)	11,534.4 (9,806.6 – 13,262.3)	
2. All cases with unknown serogroup changed from non-B to B group	B	B	B (n=93)	21,488.9 (17,841.3 – 25,136.6)	<0.001
			Non-B (n=12)	17,664.6 (14,666.1 – 20,663.1)	
3. Laboratory confirmed cases with unknown serogroup changed from non-B to B group & clinically diagnosed cases removed from analyses	B	Missing data (excluded from analysis)	B (n=87)	21,741.8 (18,240.6 – 25,243.1)	<0.001
			Non-B (n=12)	17,655.1 (14,735.0 – 20,575.3)	
4. All cases with unknown serogroup removed from analyses	Missing data (excluded from analysis)	Missing data (excluded from analysis)	B (n=75)	24,395.0 (19,997.8 – 28,792.1)	<0.001
			Non-B (n=12)	13,646.6 (11,460.2 – 15,833.0)	

Table 6: One-way sensitivity analysis results of inpatient costs during IMD RELATED READMISSIONS (for patients with sequelae only)

Scenario	Allocation		Adjusted Inpatient Costs		
	Laboratory confirmed cases with unknown serogroup (n=4)	Clinically diagnosed cases (n=1)	Serogroup	Mean costs 95% CI	p-value
Base case	Non-B	Non-B	B (n=31)	14,124.2 (8,513.5 – 19,734.9)	<0.001
			Non-B (n=10)	262.7 (202.7 – 322.7)	
1. Clinically diagnosed cases removed from analyses	Non-B	Missing data (excluded from analysis)	B (n=31)	14,596.9 (6,838.7 – 22,355.0)	<0.001
			Non-B (n=9)	415.1 (394.9 – 435.3)	
2. All cases with unknown serogroup changed from non-B to B group	B	Serogroup B	B (n=36)	12,500.9 (5,724.4 – 19,277.3)	<0.001
			Non-B (n=5)	527.8 (490.2 – 565.5)	
3. Laboratory confirmed cases with unknown serogroup changed from non-B to B group & clinically diagnosed cases removed from analyses	B	Missing data (excluded from analysis)	B (n=35)	12,247.7 (7,106.7 – 17,388.7)	<0.001
			Non-B (n=5)	386.0 (292.0 – 480.1)	
4. All cases with unknown serogroup removed from analyses	Missing data (excluded from analysis)	Missing data (excluded from analysis)	B (n=31)	13,619.7 (8,103.1 – 19,136.4)	<0.001
			Non-B (n=5)	400.2 (303.1 – 497.3)	

4.5 DISCUSSION

Our study shows IMD is associated with high health care costs, as the mean adjusted cost of acute admissions (AUD $12,312) is considerably higher than the average cost per casemix-adjusted separations in public hospitals of AUD $4,918 in 2010–11.[39] A number of studies were previously conducted in the US to assess the costs of IMD. Direct hospital costs of 1654 IMD cases were analysed by age group [22] and the costs of acute hospitalisation and follow-up care up to one year were estimated retrospectively.[21] In addition, the costing results of patients with or without sequelae were compared retrospectively in two studies [9, 11] with another study estimating the length of hospital stay and the costs of hospitalisation in children, adolescents and young adults.[20] Furthermore, lifetime sequelae costs associated with meningitis were evaluated in Senegal.[40] Consistent with findings of all these studies, our study demonstrated that IMD has profound economic as well as clinical consequences for Australian children. However our study assessed for the first time, specifically the financial burden of serogroup B related IMD. Our study results indicated IMD cases with serogroup B infection had a higher rate of health care utilisation compared to non-B serogroup cases. Previous studies did not identify or compare costs related to serogroup.

The acute hospitalisation and rehospitalisation incurred significantly higher costs for patients with sequelae than those without sequelae, which are consistent with the previous research in the US.[9, 11] These studies revealed that risk-adjusted total costs during a one year follow-up period were almost two or three times higher in patients with sequelae than those without sequelae, whereas our study

showed the magnitude of the cost differential was higher (more than four times), which might be due to different patient characteristics, especially age.

In comparison with children aged above one year, infants under one year of age had higher adjusted inpatient costs and hospital days. The US study estimating hospital costs, LOS and mortality in IMD children supports this finding.[20] Conversely, in another US study, the highest cost was associated with adolescents aged between 11 to 17 years with the lowest cost observed in infants aged less than one year.[22] However, the authors acknowledged that their sample was under-representative of infants with only 6% of patients being infants. Our study sample is reflective of the national surveillance data showing 14% of laboratory confirmed IMD patients were infants aged less than one year.[18] Adolescents aged 16 or 17 years may be admitted to a general adult hospital directly instead of being managed in a paediatric hospital, which may explain the higher proportion of infants in our study. These study findings on financial costs may be helpful to policy makers to inform future decisions about inclusion of the MenB vaccine in funded vaccination programs or target age groups for vaccination.

Since previous research used health administration databases and admissions categorised by meningitis, septicaemia and other meningococcal infections, our results regarding diagnosis groups are not comparable to those in the previous studies.[20-22]

The risk-adjusted inpatient costs and LOS were higher for children with a previous medical diagnosis. As expected underlying medical conditions may complicate

inpatient management and prolong hospital stay. However, for children with sequelae, this finding was not supported. The conflicting outcomes may result from the small sample size in the subgroup analysis. Again, there are limited studies for comparison with our research findings.

Our study had important strengths: the data were collected from a hospital database of real clinical cases over a ten year period and verified against medical notes and laboratory results with no coding errors; hospital service costs were compared between serogroup B and non B disease which was not achievable in the previous research due to lack of serotype data; to the best of our knowledge, this is the first cost of illness study of IMD conducted in Australia and therefore our results would assist local health authorities and health economists in decision making and future economic analyses.

Our study has limitations of a retrospective study design including imperfect hospital records, and missing data due to loss to follow-up. The study is also subject to the potential biases associated with observational study designs. However, we used appropriate multivariate regression analyses and robust statistical analyses and included a range of covariates, known to be significant predictors of outcome, to minimise bias. Nearly one third of patients were categorised as non-B in our study. However, serogroup was unknown in a considerable number of serogroup non-B patients. Given the likelihood that the unknown serogroup might be predominantly serogroup B, sensitivity analyses were performed to include cases with unknown serogroup in the serogroup B group. Cases with unknown serogroup were also removed from the analyses to

examine the impact of parameter uncertainty. The sensitivity analyses provide reassurance to us that the observed association between high inpatient costs and serogroup B is valid. As our study only assessed the inpatient costs and hospital stay incurred at this tertiary paediatric hospital, the direct hospital costs were underestimated without inclusion of other potential IMD related readmissions occurring at any other hospitals following the acute admission. Furthermore, indirect costs are essential to evaluate the actual financial burden of the disease, as a cost of meningitis study showed 90% of total costs resulted from productivity loss.[40] In addition, the small sample size and the fact that all data were collected from a single tertiary paediatric institution, limited generalisation of our results, which warrants further investigation of the impact of serogroup B IMD in a multicentre national study.

Despite the rarity of meningococcal disease, it imposes significant clinical and financial burden on the individuals and healthcare system, which need to be understood by the public, healthcare authorities and policy makers. To introduce a new national vaccination program, policy makers need to take into account a range of factors including vaccine safety, effectiveness and costs. Since our study has managed to assess serogroup B cases separately, the research findings provide useful insight into the impact of serogroup B disease regarding the clinical outcomes, inpatient costs and length of hospital stay, which can be used in the economic evaluation of vaccination strategies against meningococcal B disease.

4.6 REFERENCES

1. Hart CA, Thomson AP. Meningococcal disease and its management in children. *BMJ*. 2006;333(7570):685-90.

2. Moore PS. Meningococcal meningitis in sub-Saharan Africa: a model for the epidemic process. *Clin Infect Dis*. 1992;14(2):515-25.

3. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. *N Engl J Med*. 2001;344(18):1378-88.

4. Schuchat A, Robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL, et al. Bacterial meningitis in the United States in 1995. *N Engl J Med.* 1997;337(14):970-6.

5. Harrison LH. Epidemiological profile of meningococcal disease in the United States. *Clin Infect Dis.* 2010;50 Suppl 2:S37-44.

6. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine.* 2009;27 Suppl 2:B51-63.

7. *The Australian Immunisation Handbook* 2013, National Health Medical Research Council, Department of Health and Ageing, Canberra.

8. Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. *Pediatrics.* 2009;123(3):e502-9.

9. Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. *Hum Vaccin.* 2011;7(4):458-65.

10. Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec, Canada, 1990-1994. *Clin Infect Dis.* 1998;26(5):1159-64.

11. Karve S, Misurski D, Miller J, Davis KL. Costs of Sequelae Associated with Invasive Meningococcal Disease: Findings from a US Managed Care Population. *Health Outcomes Res Med.* 2011; 2: e215-e226.

12. Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. *Lancet Neurol*. 2012;11(9):774-83.

13. Peltola H. Meningococcal disease: still with us. *Rev Infect Dis.* 1983;5(1):71-91.

14. Notification Rate of Meningococcal disease (invasive), Australia, 2012 by age group and sex [database on the Internet]. Department of Health and Ageing [accessed 23 July 2013]. Available from: http://www9.health.gov.au/cda/source/rpt_5.cfm.

15. Meningococcal disease prevention and control strategies for practice-based physicians (Addendum: recommendations for college students). Committee on Infectious Diseases. *Pediatrics.* 2000;106(6):1500-4.

16. Dang V, Jamieson FB, Wilson S, Rawte P, Crowcroft NS, Johnson K, et al. Epidemiology of serogroup B invasive meningococcal disease in Ontario, Canada, 2000 to 2010. *BMC Infect Dis.* 2012;12:202.

17. Annual report of the Australian Meningococcal Surveillance Programme, 2001. *Commun Dis Intell Q Rep.* 2002;26(3):407-18.

18. Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2011. *Commun Dis Intell Q Rep.* 2012;36(3):E251-62.

19. Joint Committee on Vaccination and Immunisation (JCVI) interim position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health; 2013 [accessed 2 September 2013]; Available from:

https://www.gov.uk/government/publications/jcvi-interim-position-statement-on-the-use-of-bexsero-meningococcal-b-vaccine-in-the-uk.

20. Davis KL, Bell TJ, Miller JM, Misurski DA, Bapat B. Hospital costs, length of stay and mortality associated with childhood, adolescent and young adult meningococcal disease in the US. *Appl Health Econ Health Policy.* 2011;9(3):197-207.

21. Davis KL, Misurski DA, Miller JM, Bell TJ, Bapat B. Cost of acute hospitalization and post-discharge follow-up care for meningococcal disease in the United States. *Hum Vaccin.* 2011;7(1):96-101.

22. O'Brien JA, Caro JJ, Getsios D. Managing meningococcal disease in the United States: Hospital case characteristics and costs by age. *Value Health.* 2006;9(4):236-43.

23. Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease: scenarios of severe meningitis and septicemia. *Paediatr Drugs.* 2013;15(1):49-58.

24. Durand-Zaleski I. Why cost-of-illness studies are important and inform policy. *Vasc Med*. 2008;13(3):251-3.

25. Ortega-Sanchez IR, Meltzer MI, Shepard C, Zell E, Messonnier ML, Bilukha O, et al. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. *Clin Infect Dis.* 2008;46(1):1-13.

26. Scott RD, Meltzer MI, Erickson LJ, De Wals P, Rosenstein NE. Vaccinating first-year college students living in dormitories for Meningococcal disease: an economic analysis. *Am J Prev Med.* 2002;23(2):98-105.

27. Shepard CW, Ortega-Sanchez IR, Scott RD, Rosenstein NE, Team AB. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. *Pediatrics.* 2005;115(5):1220-32.

28. Skull SA, Butler JR. Meningococcal vaccination for adolescents? An economic evaluation in Victoria. *J Paediatr Child Health.* 2001;37(5):S28-33.

29. Trotter CL, Edmunds WJ. Modelling cost effectiveness of meningococcal serogroup C conjugate vaccination campaign in England and Wales. *BMJ*. 2002;324(7341):809.

30. Trotter CL, Edmunds WJ. Reassessing the cost-effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model. *Med Decis Making*. 2006;26(1):38-47.

31. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine.* 2013;31(23):2638-46.

32. Miller MA, Shahab CK. Review of the cost effectiveness of immunisation strategies for the control of epidemic meningococcal meningitis. *Pharmacoeconomics.* 2005;23(4):333-43.

33. Wang B, Clarke M, Thomas N, Howell S, Haji Ali Afzali H, Marshall H. The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children (in press). *Pediatr Infect Dis J*.

34. 6401.0 Consumer Price Index, Australia. TABLE 11. CPI: Group, Sub-group and Expenditure Class, Index Numbers by Capital City. Australian Bureau of Statistics; 2012 [accessed 12 Jan 2013]; Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/6401.0Sep%202012.

35. Davison AC. Bootstrap methods and their application. Cambridge: Cambridge University Press; 1997.

36. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The disease burden of invasive meningococcal serogroup B disease in Canada. *Pediatr Infect Dis J*. 2013;32(1):e20-5.

37. Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Serv Res Policy.* 2004;9(4):197-204.

38. Basu A, Manning WG. Issues for the next generation of health care cost analyses. *Med Care.* 2009;47(7 Suppl 1):S109-14.

39. Hospital performance: cost per casemix-adjusted separation. Australian Institute of Health and Welfare 2013; 2013 [Accessed 16 July 2013]; Available from: http://www.aihw.gov.au/haag10-11/hospital-performance-cost/.

40. Griffiths UK, Dieye Y, Fleming J, Hajjeh R, Edmond K. Costs of meningitis sequelae in children in Dakar, Senegal. *Pediatr Infect Dis J.* 2012;31(11):e189-95.

Based on this study, it can be concluded that although IMD is uncommon, the severe outcomes of the disease and long-term management of sequelae imposes significant financial burden on the health care system. Since health economic assessments play an important role in decision making on public funding allocations, our study results can provide valuable information to health economists when an economic evaluation model is required to assess cost-effectiveness of a new MenB vaccine program. Moreover, our study results can inform policy makers by revealing a rough estimation of the cost saving and the medical benefits of a new meningococcal vaccination program.

CHAPTER 5: COMMUNITY, PARENTAL AND ADOLESCENT AWARENESS AND KNOWLEDGE OF IMD

Survey results of the general public's view of IMD are presented in an article entitled "Community, parental and adolescent awareness and knowledge of meningococcal disease". The article has been accepted by the journal "Vaccine" (see appendix 2).

Literature shows that parents' perception of disease severity and susceptibility to disease could play an important role in parental acceptance of a relevant vaccine. Moreover, lack of disease specific knowledge could result in poor compliance with new vaccination programs. Adolescents are likely to be a target group of a new MenB vaccine due to high incidence and carriage rates. However, there is limited information available on Australian community views on IMD, particularly in adolescents. Hence, our study aims to assess knowledge of IMD and concern about the disease in the Australian Community including adolescents, adults, parents and non-parents.

The first question is an open ended question, assessing knowledge about IMD in general. Another three questions examined knowledge of severity and incidence of and susceptibility to IMD. A scoring system has used to grade knowledge of IMD for analysis. Based on the results of these three questions, an overall score of IMD knowledge was calculated for each participant. If a participant responded to two of three questions correctly, two scores were given to this participant. The last question asked how concerned participants were about IMD. All results of knowledge, overall scores and concerns were dichotomised as binary outcomes

(e.g. lower or higher, incorrect or correct). Considerable knowledge gaps were identified in the study (Supplementary Table 1). More than one third of participants only answered one question correctly or all questions incorrectly. Although IMD could result in severe outcomes such as death, amputations and neurological deficits, 66.6% expressed low concern about IMD. However, the low concern about IMD may reflect an appreciation of low risk of the disease, as IMD is a rare condition mainly affecting children and adolescents with a low incidence rate.

We identified a number of socio-demographic factors associated with responding correctly or incorrectly to questions on severity and incidence of and susceptibility to IMD (Supplementary Tables 2 – 4). Adolescents were less likely to understand severity and incidence of the disease correctly compared with adults. Results of overall scores and concern are outlined in the article.

Title: Community, parental and adolescent awareness and knowledge of meningococcal disease

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NOTE:
Statements of authorship appear on page 141 in the print copy of the thesis held in the University of Adelaide Library.

5.1 ABSTRACT

Objective: To assess knowledge of invasive meningococcal disease (IMD) and concern about the disease in the Australian Community including adolescents, adults, parents and non-parents.

Design and setting: This cross-sectional study was conducted by face to face interviews in South Australia in 2012. Participants were scored on their knowledge and concern about IMD. Univariate and multivariate regression analyses were performed with the survey data weighted by age and gender in accordance with 2011 Census data.

Participants: Of 5,200 households randomly selected and stratified by metropolitan or rural location, 3,055 participants were interviewed with a response rate of 60.3%.

Main outcome measures: An overall score of knowledge of IMD and concern about the disease.

Results: The majority were Australian born (74.2%, n=2,267) with 31.8% (n=972) of those interviewed being parents, and 15.9% (n=487) adolescents (15 – 24 years). Adult (non-adolescent) participants ($p<0.050$), Australian born ($p<0.001$), tertiary educated ($p=0.019$), high household income ($p=0.011$), high socio-economic status ($p=0.003$) or living in a rural residential area ($p=0.006$) were more likely to have higher overall knowledge of IMD. Participants who were not parents ($p<0.001$), male gender ($p<0.001$), single ($p<0.001$), highly educated ($p=0.022$) or

had high household income (p=0.015), were associated with lower concern about IMD.

Conclusion: Large community knowledge gaps about IMD were observed, particularly amongst adolescents and adults with lower educational attainment and lower socio-economic status. Improving community knowledge of IMD could help ensure optimal uptake of new meningococcal vaccines. Our study results can help guide development of community tailored immunisation education programs.

5.2 INTRODUCTION

Invasive meningococcal disease (IMD) is characterised by its rapid onset, high case fatality, high rate of incapacitating long-term sequelae, and is a leading infectious cause of death in childhood in industrialised countries.[1] The highest disease incidence occurs in children < 5 years and adolescents 15 – 24 years of age.[2] Clinical disease such as meningitis and septicaemia are caused by six of thirteen *Neisseria meningitidis* subgroups (A, B, C, W135, X and Y). Meningococcal vaccines are currently available in Australia to protect against meningococcal serogroups A, C, W135 and Y.[3] However, approximately 85% of serogroup-confirmed meningococcal cases are now caused by serogroup B, as the number of cases of other serogroups, particularly serogroup C, has declined since the implementation of universal meningococcal C childhood vaccination.[4, 5] A new meningococcal B (MenB) vaccine, Bexsero®, has recently been approved in the EU and Australia for use in individuals from two months of age. The Joint Committee on Vaccination and Immunisation (JCVI) in the UK is currently considering the potential for inclusion of Bexsero® in the National Immunisation Program.[6] An interim position statement from the JCVI has recommended the MenB vaccine to not be included in the UK funded routine immunisation program,[7] with further advice from stakeholders currently under review.[8-17] In its meeting in November 2013, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia did not recommend the inclusion of the multicomponent meningococcal B vaccine on the National Immunisation Program Schedule mainly because of its unfavourable cost-effective estimate, uncertain assumptions about vaccine effectiveness and large vaccination coverage required.[18] A resubmission is planned to address issues raised by the PBAC.[19]

Awareness and attitudinal research can not only give us in-depth insights into the general public's knowledge about IMD but can also provide useful information to regulatory authorities when considering funding and introduction of a new vaccination program. Such research enables us to understand motivations, barriers, and other influential factors affecting vaccine implementation and also allow us to recognise the needs of different population groups.[20] Finding out public perception of the seriousness of the disease to be prevented by a new vaccine and addressing inaccuracies through targeted education and promotion, are imperative to achieving high coverage of a new vaccine[21], with consequential impact on its cost-effectiveness analysis. Surveys to evaluate the views of stakeholders and target groups are valuable for identifying challenges and opportunities prior to implementing a vaccination program.[22] Previous studies have indicated that public recognition of disease severity could play an important role in parental acceptance of a relevant vaccine.[23] Conversely, lack of disease specific knowledge could lead to poor compliance with new vaccines.[24, 25] The assessment of community knowledge and awareness of IMD is required to understand the general public's view of the disease in order to help decision makers and immunisation educators to develop community tailored educational programs and therefore to maximise vaccine coverage. High uptake of a vaccine with potential herd immunity benefits can affect cost-effectiveness results [26] and would also be an important consideration in vaccine funding decision-making.

There is currently limited information regarding community, parental and adolescent knowledge and awareness of IMD. An online survey was conducted in

seven countries including Australia, to investigate health care providers' and parents' knowledge and attitudes toward vaccine-preventable disease and introduction of new vaccines in infants.[27] The new MenB vaccine was used as an example to detect factors impacting vaccine decisions. It was concluded that improving awareness of the vaccine-preventable disease would be essential for a high vaccine uptake. As an online survey, study results were subject to selection bias with limited generalisability of the study results.

Two other studies in the Netherlands and Auckland have also assessed parental awareness of IMD. These studies suggested that the vast majority of parents were aware of the severity of IMD and that perceived vulnerability was associated with a more positive attitude towards vaccination. However, the response rate is poor and these studies are both limited by selection bias. Thus, the study results may not be generalisable to the population.[28-30]

This current, large population study aimed to assess knowledge and concern about IMD and perception of disease severity, incidence and susceptibility in the Australian community and determine factors associated with lower or higher knowledge and concern.

5.3 METHODS

This cross-sectional study was conducted by face to face interviews in South Australia. 5,200 households were randomly selected according to the collectors' districts used by the Australian Bureau of Statistics in the 2006 Census and stratified by metropolitan or rural location.[31]

Questions were asked to assess general understanding and perception of severity, incidence and susceptibility to IMD, and concerns about IMD (Figure 1). Detailed demographic details were collected including age, gender, country of birth, marital status, family composition, educational attainment, work status and household income.

Figure 1 Interview questions on understanding and concern about IMD

General Understanding of IMD
• What do you understand by the term 'meningococcal disease'? (open-ended question)
Understanding of severity of IMD
• Which do you believe best describe your understanding of meningococcal disease in terms of severity? 1. Mild disease 2. Moderately Severe (may require hospitalisation) 3. Severe (requires hospitalisation) 4. Very Severe (may be life threatening or fatal) 5. Don't know/Unsure
Understanding of incidence of IMD
• Which do you believe best describe your understanding of meningococcal disease in terms of incidence? 1. Rare (affects less than 1/1000 people) 2. Uncommon (affects less than 1/100 people) 3. Common (affects more than 1/100 people) 4. Very common (affects more than 1/10 people) 5. Don't know/Unsure
Understanding of susceptibility to IMD
• Which do you believe best describe your understanding of meningococcal disease in terms of people affected? 1. Mostly children 2. Mostly adolescents 3. Mostly children or adolescent 4. Mostly elderly 5. Mostly people with other medical conditions 6. Any age equally 7. Don't know/Unsure
Overall concern about IMD
• On a scale of 0 – 10 where 0 means you are not concerned at all and 10 means you are extremely concerned, how concerned are you about meningococcal disease? Enter number 0 – 10 ☐☐ or R for "Refused"

Statistical analyses were performed using Stata, version 11 (StataCorp) with the survey data weighted in accordance with 2011 Census figures to provide a demographic description of the South Australian population by age and gender. The weighting process ensured our findings were representative of the South Australian population as a whole.

The outcome measures included an overall score of knowledge of IMD and concern about the disease. Answers to three questions on knowledge of severity, incidence and susceptibility to IMD were dichotomised as "correct" or "incorrect".

When the participant chose a correct answer to one question, one score was given to the participant. The overall score was calculated as the total scores of these three questions. Participants who answered at least two of these three questions correctly were considered to have a higher overall score (2 – 3). An overall score less than two was categorised as a lower overall score (0 – 1). The participants were asked to assess their concern about IMD on a scale of 0 to 10 with an opt-out option “refused” or “don’t know”. A level of 6 – 10 was classified as “higher concern” and a level of 0 – 5 was classified as “lower concern”.

The predictor variables were comprised of country of birth, marital status, educational attainment, work status, household income, gender, age, geographical area, socio-economic status and parental status of the participants (whether the participants were parents or not in the household). The levels of socio-economic status were determined by the Socio Economic Index for Areas (SEIFA) Index of Relative Socioeconomic Disadvantage.[32]

Univariate and multiple logistic regression analyses were performed to test association between predictor variables and outcome measures. Any above-mentioned covariates with a p-value ≤ 0.20 on a univariate analysis of association with an outcome measure, were included into a multivariate logistic model. All results presented in the univariate and multivariate analyses were weighted. A two-sided p-value of less than 0.05 was deemed to be statistically significant.

The study was approved by the Women's and Children's Health Network Human Research Ethics Committee and the University of Adelaide Human Research Ethics Committee.

5.4 RESULTS

5.4.1 Study population

Among 5,200 randomly selected households, 137 were not permanent tenants and were excluded. Of the remaining 5063 households, 3,055 participants were interviewed with a response rate of 60.3%. 2008 households did not complete interviews due to various reasons (refusal (n=1178), contact not being established after six attempts (n=460), mental incapacity (n=94), non-English speaker (n=88), other (n=188)). Interviews were conducted between 4th September and 12th December 2012. Over half the participants were Australian born (74.2%, n=2,267) and 54.6% were employed (n=1,668). Approximately 70% of households (n=2,131) did not contain children and one third of participants (31.8%, n=972) were parents in the households. 15.9% of participants (n=487) were adolescents aged 15 – 24 years (Table 1).

Table 1: Socio-demographic characteristics

Variables	Number	Percent	95% CI	Weighted Number	Weighted Percent	95% CI
Age						
15 – 24 (adolescents)	306	10.0	9.0 – 11.1	487	15.9	14.2 – 17.7
25 – 54 (young and middle aged adults)	1,389	45.5	43.7 – 47.2	1,501	49.1	47.1 – 51.2
55+ (older adults)	1,360	44.5	42.8 – 46.3	1,066	34.9	33.1 – 36.7
Gender						
Male	1,279	41.9	40.1 – 43.6	1,494	48.9	46.9 – 50.9
Female	1,776	58.1	56.4 – 59.9	1,561	51.1	49.1 – 53.1
Country of birth						
Non-Australia	792	25.9	24.4 – 27.5	787	25.8	24.0 – 27.5
Australia	2,262	74.1	72.5 – 75.6	2,267	74.2	72.5 – 76.0
Marital Status						
Married/De Facto	1,719	56.3	54.6 – 58.1	1,905	62.4	60.5 – 64.4
Single	1,333	43.7	41.9 – 45.4	1,147	37.6	35.6 – 39.5
Educational attainment						
Lower than Year 12 education	1,113	36.5	34.8 – 38.2	1,063	34.8	32.9 – 36.7
Higher than or equal to Year 12 education trade/ certificate/diploma	1,281	42.0	40.3 – 43.8	1,307	42.8	40.9 – 44.8
Degree or higher	655	21.5	20.0 – 22.9	682	22.3	20.7 – 24.0
Work status						
Employed	1,561	51.1	49.3 – 52.9	1,668	54.6	52.6 – 56.6
Unemployed	288	9.4	8.4 – 10.5	300	9.8	8.6 – 11.0
Retired	850	27.8	26.2 – 29.4	614	20.1	18.7 – 21.5
Student	192	6.3	5.4 – 7.1	330	10.8	9.3 – 12.3
Other	163	5.3	4.5 – 6.1	144	4.7	3.9 – 5.5
Household income						
Low (≤ AUD $40,000)	820	36.5	34.5 – 38.5	583	27.7	25.8 – 29.6
Medium (AUD $40,001 – $80,000)	603	26.9	25.0 – 28.7	582	27.6	25.6 – 29.7
High (≥ AUD $80,001)	821	36.6	34.6 – 38.6	941	44.7	42.3 – 47.0
Area						
Metropolitan	2,241	73.4	71.8 – 74.9	2,235	73.2	71.4 – 75.0
Rural	814	26.6	25.1 – 28.2	820	26.8	25.0 – 28.6
Socio-economic status						
Low (1^{st} – 33^{rd} percentile)	1,144	37.4	35.7 – 39.2	1,160	38.0	36.0 – 39.9
Medium (34^{th} – 66^{th} percentile)	938	30.7	29.1 – 32.3	907	29.7	27.9 – 31.5
High (67^{th} – 100^{th} percentile)	973	31.8	30.2 – 33.5	988	32.3	30.5 – 34.2
Total number of children in household						
0	2,131	69.8	68.1 – 71.4	2,131	69.8	68.1 – 71.4
1	346	11.3	10.2 – 12.5	346	11.3	10.2 – 12.5
2	397	13.0	11.8 – 14.2	397	13.0	11.8 – 14.2
3+	180	5.9	5.1 – 6.7	180	5.9	5.1 – 6.7
Total number of people in household						
1	759	24.8	23.3 – 26.4	759	24.8	23.33 – 26.4
2	1,138	37.3	35.5 – 39.0	1,138	37.3	35.5 – 39.0
3	432	14.1	12.9 – 15.4	432	14.1	12.9 – 15.4
4	477	15.6	14.3 – 16.9	477	15.6	14.3 – 16.9
5+	249	8.2	7.2 – 9.1	249	8.2	7.2 – 9.1
Participant's parental status						
No	2,220	72.7	71.1 – 74.3	2,080	68.2	66.2 – 70.1
Yes	834	27.3	25.7 – 28.9	972	31.8	29.9 – 33.8

5.4.2 General understanding of IMD

Almost a quarter of participants (23.5%, n=717) had no knowledge of IMD and 15.9% (n=486) understood that IMD was a bacterial infection with almost 10% of participants (n=278) believing incorrectly that IMD was a viral infection. There was a large variety of answers to the question "What do you understand by the term 'meningococcal disease'?" with the majority of people able to identify some characteristics of IMD. Although IMD is rare, there was evidence of a close association with a case for two participants, one who described that their grandson had died of IMD with another participant indicating they knew a girl who underwent amputation of her arms and legs following IMD. Just over a quarter of participants (30.4%, n=930) described IMD as "deadly", "serious" or "severe" infection (Table 2).

Table 2 General understanding of IMD

General understanding of IMD	Number	Percent	95% CI	Weighted Number	Weighted Percent	95% CI
Don't know	654	21.4	20.0 – 22.9	717	23.5	21.7 – 25.3
Bacterial infection that can be deadly	490	16.1	14.8 – 17.4	486	15.9	14.5 – 17.4
Meningitis - inflammation in the tissue	447	14.6	13.4 – 15.9	419	13.7	12.4 – 15.1
Virus/viral infection	286	9.4	8.3 – 10.4	278	9.1	8.0 – 10.3
Rash/spots/fever	270	8.8	7.8 – 9.9	260	8.5	7.4 – 9.6
Life threatening/deadly	223	7.3	6.4 – 8.2	212	6.9	6.0 – 7.9
Others	157	5.1	4.4 – 5.9	165	5.4	4.5 – 6.3
Serious/dangerous/ severe	118	3.9	3.2 – 4.6	119	3.9	3.2 – 4.7
Severe infection resulting in amputation	110	3.6	2.9 – 4.3	113	3.7	2.9 – 4.4
Flesh eating infection	105	3.4	2.8 – 4.1	103	3.4	2.7 – 4.1
Brain disease/affects brain	54	1.8	1.3 – 2.2	51	1.7	1.2 – 2.2
Waterborne infection	31	1.0	0.7 – 1.4	27	0.9	0.5 – 1.2
Affects young people	30	1.0	0.6 – 1.3	29	0.9	0.6 – 1.3
Blood disease/affects blood	27	0.9	0.6 – 1.2	25	0.8	0.5 – 1.2
Flu like illness	20	0.7	0.4 – 0.9	20	0.7	0.3 – 1.0
An infection	15	0.5	0.2 – 0.7	13	0.4	0.2 – 0.7
Contagious	15	0.5	0.2 – 0.7	14	0.5	0.2 – 0.7

5.4.3 Overall knowledge of IMD

In total, 63.4% of participants (n=1,933) answered at least two of three questions on severity, incidence and susceptibility to IMD correctly and were classified as having higher knowledge with 27.1% (n=827) answering only one question correctly and 9.4% (n=288) responding to all questions incorrectly.

The majority (87.2%, n=2,661) understood correctly that IMD was a severe or very severe disease. Birth country not Australia ($p<0.001$), single status ($p=0.008$), having not completed school ($p=0.006$), low household income ($p<0.050$), male gender ($p<0.001$), adolescents ($p<0.050$) or metropolitan residential area ($p=0.038$), were associated with a lower odds of responding correctly to the question on IMD severity. Most participants (69.6%, n=2,126) were incorrect in their knowledge of the incidence of IMD: 35.2% (n=1,074) answering that IMD was uncommon (incidence rate <1/100), but not rare (incidence rate <1/1000), 19.3% (n=589) believing that IMD was common (incidence rate >1/100), and 13.4% (n=409) not able to answer the question and 1.8% (n=53) considering IMD as "very common" (incidence rate >1/10). Participants born in Australia ($p=0.010$), completed tertiary education ($p<0.050$), high household income ($p<0.050$), male gender ($p<0.001$), age of 25 – 54 years ($p=0.020$) or higher socio-economic status ($p=0.003$) were more likely to answer the question on IMD incidence correctly. More than half (55.3%, n=1,689) gave a correct answer to the question on IMD susceptibility and agreed children and/or adolescents were the main groups affected, with one third (30.4%, n=929) describing incorrectly that IMD affected any age equally and 12.0% (n=367) being uncertain of the answer. Female gender ($p=0.004$), rural residential area ($p=0.003$), and high socio-economic status

(p<0.050) were predictors of answering the question on age group susceptibility correctly.

After adjusting for socio-demographic covariates, non-adolescents (p<0.050), being born in Australia (p<0.001), tertiary education (p=0.019), high household income (p=0.011), rural residential area (p=0.006) and high socio-economic status (p=0.003) were significantly associated with a higher overall score of IMD knowledge (Table 3). No difference in levels of overall IMD knowledge was found between parents and non-parents (OR: 1.00 (95% CI: 0.75 – 1.33), P=0.996).

Table 3 Predictors of participants with good overall understanding of meningococcal disease*

Variables	Participants with a higher overall score (2-3)		Participants with a lower overall score (0-1)		Univariate Associations			Multivariate Logistic Regression Analysis		
					Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	95% CI	p-value
Age	**n**	**%**	**n**	**%**			**<0.001**			**0.067**
15 – 24 (adolescents)	219	45.1	266	54.9	1.00	-		-	-	-
25 – 54 (young and middle aged adults)	1,019	68.0	480	32.0	2.59	1.97 – 3.40	<0.001	1.68	1.07 – 2.64	0.023
55+ (older adults)	695	65.4	368	34.6	2.30	1.75 – 3.02	<0.001	1.69	1.03 – 2.77	0.038
Gender	**n**	**%**	**n**	**%**						
Male	937	62.9	553	37.1	1.00	-		-	-	-
Female	996	64.0	561	36.0	1.05	0.88 – 1.24	0.586	-	-	-
Country of birth	**n**	**%**	**n**	**%**						
Non-Australia	420	53.5	366	46.5	1.00	-		-	-	
Australia	1,152	66.9	749	33.1	1.76	1.46 – 2.12	<0.001	1.55	1.23 – 1.98	<0.001
Marital Status	**n**	**%**	**n**	**%**						
Married/De Facto	1,289	67.8	612	32.2	1.00	-		-	-	
Single	643	56.2	501	43.8	0.61	0.51 – 0.72	<0.001	0.99	0.79 – 1.25	0.939
Educational attainment	**n**	**%**	**n**	**%**			**<0.001**			**0.055**
Lower than Year 12 education	601	56.7	459	43.3	1.00	-		-	-	
Higher than or equal to Year 12 education/trade/ certificate/diploma	842	64.6	461	35.4	1.39	1.15 – 1.69	0.001	1.22	0.96 – 1.56	0.099
Degree or higher	489	71.8	192	28.2	1.95	1.53 – 2.48	<0.001	1.47	1.06 – 2.02	0.019
Work status	**n**	**%**	**n**	**%**			**<0.001**			**0.660**
Employed	1,232	68.0	532	32.0	1.00	-		-	-	
Unemployed	179	59.8	120	40.2	0.70	0.52 – 0.94	0.016	0.93	0.64 – 1.35	0.709
Retired	388	63.3	225	36.7	0.81	0.67 – 0.98	0.033	1.16	0.81 – 1.64	0.418
Student	150	45.6	179	54.4	0.39	0.28 – 0.55	<0.001	0.81	0.45 – 1.45	0.474
Other	84	59.2	58	40.8	0.68	0.47 – 0.99	0.044	0.85	0.53 – 1.35	0.482
Household income	**n**	**%**	**n**	**%**			**<0.001**			**0.039**
Low (≤ AUD $40,000)	365	62.9	215	37.1	1.00	-		-	-	
Medium (AUD $40,001 – $80,000)	398	68.4	184	31.6	1.28	0.99 – 1.64	0.056	1.25	0.93 – 1.67	0.135
High (≥ AUD $80,001)	699	74.5	239	25.5	1.72	1.36 – 2.18	<0.001	1.53	1.10 – 2.14	0.011
Area	**n**	**%**	**n**	**%**						
Metropolitan	1,394	62.6	835	37.4	1.00	-		-	-	
Rural	539	65.8	280	34.2	1.15	0.95 – 1.40	0.155	1.44	1.11 – 1.87	0.006
Socio-economic status	**n**	**%**	**n**	**%**			**0.001**			**0.006**
Low (1st – 33rd percentile)	692	59.8	465	40.2	1.00	-		-	-	
Medium (34th – 66th percentile)	564	62.4	341	37.6	1.11	0.91 – 1.36	0.303	1.06	0.82 – 1.36	0.672
High (67th – 100th percentile)	676	68.7	309	31.3	1.47	1.20 – 1.81	<0.001	1.54	1.16 – 2.05	0.003
Participant's parental status	**n**	**%**	**n**	**%**						
No	1,293	62.3	782	37.7	1.00	-		-	-	-
Yes	637	65.7	333	34.3	1.16	0.96 – 1.40	0.130	1.00	0.75 – 1.33	0.996

* All results were weighted.

Adolescents had poor knowledge of IMD including severity (OR: 0.34 (95% CI: 0.18 – 0.64), p=0.001), incidence (OR: 0.56 (95% CI: 0.33 – 0.94), p=0.028) and susceptibility to IMD (OR: 0.86 (95% CI: 0.56 – 1.33), p=0.493) in comparison with adults aged ≥ 25 years after adjusting other covariates. In general, adolescents were less likely to gain a higher score of overall IMD knowledge (OR: 0.59 (95% CI: 0.38 – 0.92), p=0.020).

5.4.4 General concern about IMD

1,922 participants (62.9%) had lower concern (a score of 0 – 5) about IMD including 19.1% (n=585) who scored concern as zero. 965 participants (31.6%) expressed higher concern (a score of 6 – 10) about the disease consisting of 9.8% (n=301) being extremely concerned (a score of 10), with 105 (3.4%) refusing and 63 (2.1%) stating “don’t know”. Participants who were not parents (p<0.001), male gender (p<0.001), single (p<0.001), highly educated (p=0.022) or had high household income (p=0.015), were more likely to have lower concern about the disease (Table 4). In addition, the level of concern about IMD was not significantly associated with overall knowledge scores (p=0.171).

Table 4 Predictors of participants with higher concern of meningococcal disease*

Variables	Participants with higher concern (6 – 10)		Participants with lower concern (0 – 5)		Univariate Associations			Multivariate Logistic Regression Analysis		
					Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	95% CI	p-value
Age	**n**	**%**	**n**	**%**			**0.001**			**0.257**
15 – 24 (adolescents)	104	23.5	340	76.5	1.00	-		-	-	
25 – 54 (young and middle aged adults)	506	35.3	927	64.7	1.78	1.29 – 2.45	<0.001	1.25	0.75 – 2.08	0.400
55+ (older adults)	355	35.1	656	64.9	1.76	1.28 – 2.43	0.001	1.52	0.88 – 2.64	0.135
Gender	**n**	**%**	**n**	**%**						
Male	374	26.7	1,204	73.3	1.00	-		-	-	
Female	591	39.7	898	60.3	1.80	1.51 – 2.16	<0.001	1.75	1.41 – 2.17	<0.001
Country of birth	**n**	**%**	**n**	**%**						
Non-Australia	213	31.0	475	69.0	1.00	-		-	-	
Australia	752	34.2	1,447	65.8	1.16	0.94 – 1.42	0.159	1.04	0.82 – 1.33	0.740
Marital Status	**n**	**%**	**n**	**%**						
Married/De Facto	696	38.1	1,130	61.9	1.00	-		-	-	
Single	268	25.3	791	74.7	0.55	0.46 – 0.66	<0.001	0.62	0.49 – 0.79	<0.001
Educational attainment	**n**	**%**	**n**	**%**			**<0.001**			**0.065**
Lower than Year 12 education	378	37.9	619	62.1	1.00	-		-	-	
Higher than or equal to Year 12 education/trade/ certificate/diploma	414	33.1	838	66.9	0.81	0.67 – 0.98	0.031	0.90	0.70 – 1.15	0.410
Degree or higher	172	27.0	465	73.0	0.61	0.47 – 0.77	<0.001	0.69	0.50 – 0.95	0.022
Work status	**n**	**%**	**n**	**%**			**<0.001**			**0.965**
Employed	532	33.3	1,064	66.7	1.00	-		-	-	
Unemployed	122	43.5	159	56.5	1.54	1.15 – 2.05	0.003	0.98	0.67 – 1.42	0.901
Retired	199	34.8	373	65.2	1.07	0.87 – 1.30	0.525	0.94	0.67 – 1.31	0.712
Student	57	19.3	239	80.7	0.48	0.31 – 0.74	0.001	0.87	0.41 – 1.85	0.722
Other	54	38.5	87	61.5	1.25	0.86 – 1.83	0.247	1.11	0.68 – 1.81	0.666
Household income	**n**	**%**	**n**	**%**			**0.008**			**0.051**
Low (≤ AUD $40,000)	221	39.9	333	60.1	1.00	-		-	-	
Medium (AUD $40,001 – $80,000)	206	36.6	357	63.4	0.87	0.68 – 1.11	0.257	0.79	0.59 – 1.05	0.110
High (≥ AUD $80,001)	290	31.7	626	68.3	0.70	0.55 – 0.88	0.002	0.65	0.47 – 0.92	0.015
Area	**n**	**%**	**n**	**%**						
Metropolitan	651	31.0	1,451	69.0	1.00	-		-	-	
Rural	314	40.0	471	60.0	1.48	1.22 – 1.80	<0.001	1.23	0.95 – 1.59	0.122
Socio-economic status	**n**	**%**	**n**	**%**			**<0.001**			**0.325**
Low (1st – 33rd percentile)	416	38.4	665	61.6	1.00	-		-	-	
Medium (34th – 66th percentile)	275	31.9	589	68.1	0.75	0.61 – 0.92	0.007	0.85	0.66 – 1.09	0.204
High (67th – 100th percentile)	274	29.1	668	70.9	0.66	0.53 – 0.81	<0.001	0.82	0.62 – 1.10	0.191
Participant's parental status	**n**	**%**	**n**	**%**						
No	563	28.9	1,387	71.1	1.00	-		-	-	
Yes	402	43.0	532	57.0	1.86	1.54 – 2.24	<0.001	2.09	1.58 – 2.78	<0.001

* All results were weighted.

5.5 DISCUSSION

Our study results revealed large knowledge gaps and sub-optimal understanding of IMD, particularly amongst adolescents. Although 87% of participants recognised correctly that IMD could be severe or very severe, a considerable number of participants were not aware of IMD or had misconceptions about the disease. As adolescents are a target group for MenB vaccination, increasing awareness and knowledge of IMD is a priority.

Our study identified a number of socio-demographic factors that were related to poor knowledge of IMD and lower concern about the disease which have previously been associated with low knowledge of vaccine preventable diseases.[33, 34] Participants with a high level of educational attainment, household income or socio-economic status were almost 1.5 times more likely to have higher overall knowledge of IMD compared with those who had low educational attainment, household income or socio-economic status.

In our study, parental status of participants was significantly associated with higher concern about IMD. A study in the Netherlands indicated parents overestimated the risk of being infected with the meningococcus and dying from IMD. This study showed that highly educated parents were less worried and had lower perceived risk of IMD infection which is consistent with our findings.[29]

Although a high level of educational attainment or household income was significantly associated with lower concern and higher scores of overall knowledge of IMD, the lower concern and a higher level of knowledge of IMD were not related,

indicating that increasing accurate disease specific knowledge may not influence concern. Previous survey studies support the finding that greater knowledge of disease is not associated with levels of anxiety or concern.[35, 36]

Female participants were almost twice as likely to have higher concern about IMD than males. A similar gender association was found in web-based and community surveys about influenza showing female parents perceived a higher threat of influenza than males.[33, 37]

Previous research has indicated health education and improvement in public awareness of vaccine-preventable disease (e.g. IMD) could increase uptake of a new vaccine.[27, 34] A survey of influenza vaccines showed that lack of disease related knowledge and a lower perceived risk from infections could lead to vaccine declination.[38] A questionnaire survey in the UK and online survey study in the US revealed knowledge of the disease, particularly severity and susceptibility, affected parental acceptance of a new vaccine.[37, 39] Our study results provide community-specific information on general awareness, knowledge of severity, incidence and susceptibility, and overall concern about IMD, which can enable policy makers and immunisation educators to develop community-tailored and appropriate educational programs once a new MenB vaccine is available. Our findings can assist in increasing awareness of the severity of IMD and correcting any misconceptions effectively by targeting simple but specific information to address these inaccuracies. Furthermore, understanding of community knowledge of the disease could be helpful for health care providers to target specific groups with less knowledge to efficiently improve uptake of a new vaccine and empower

individuals to make more informed decisions around vaccination. Vaccination coverage rates affect economic evaluations of vaccines[40] and high uptake of a vaccine with potential indirect population protection could add extra benefits to a vaccination program.[26]

Our study had several important strengths. Firstly, a large number of participants were randomly selected from the South Australian population and the survey data were weighted to report on the population level improving generalisability of our findings. In addition, we were able to assess adolescent's knowledge of meningococcal disease, an important target group for MenB immunisation. Furthermore, in-depth socio-demographic data were collected which were essential to investigate which socio-demographic groups had low knowledge and awareness of IMD. Lastly, as the survey was conducted through face to face interviews, results are likely to be an accurate representation of knowledge. However, the limitation of face to face interviews is that participants may respond in a socially acceptable way, which may bias the study results. This was a cross sectional study and therefore has some limitations. The survey was conducted in 2012 prior to licensing of the meningococcal vaccine against serogroup B disease. News and new promotional programs may raise public awareness of the disease. Non-English speakers were not included in the study. Nonetheless, the proportion of non-English speakers excluded from the study was small, so is likely to have limited impact on the study results.

As serogroup B IMD predominates in Australia, accounting for around 85% of IMD cases in 2011,[5] high uptake of the new MenB vaccine would be required to

reduce the incidence of IMD and relieve the economic burden of the disease. The delivery of community tailored educational programs and informational materials can help to achieve high coverage by targeting those with the least knowledge and lowest concern about IMD once a MenB vaccine is available. If Bexsero® is not funded on the National Immunisation Program but is available on the private market, community perceptions and understanding are key to vaccine intake.

Supplementary Table 1 Knowledge of severity and incidence of and susceptibility to IMD and level of concern about IMD

Outcomes	Level	Number	Percent	95% CI	Weighted Number	Weighted Percent	95% CI
Knowledge of severity of IMD							
	Incorrect	349	11.4	10.3 – 12.6	391	12.8	11.4 – 14.3
	Correct	2,703	88.6	87.4 – 89.7	2,661	87.2	85.7 – 88.6
Knowledge of incidence of IMD							
	Incorrect	2,102	68.9	67.2 – 70.5	2,126	69.6	67.8 – 71.4
	Correct	951	31.1	29.5 – 32.8	928	30.4	28.6 – 32.2
Knowledge of susceptibility to IMD							
	Incorrect	1,334	43.7	42.0– 45.5	1,362	44.7	42.6 – 46.7
	Correct	1,716	56.3	54.5 – 58.0	1,689	55.3	53.3 – 57.4
Overall score of knowledge of IMD							
	Low (0 – 1)	1,069	35.1	33.4 – 36.8	1,114	36.6	34.6 – 38.5
	High (2 – 3)	1,978	64.9	63.2 – 66.6	1,933	63.4	61.5 – 65.4
Level of concern about IMD							
	Low (0 – 5)	1,920	66.3	64.6 – 68.0	1,922	66.6	64.6 – 68.5
	High (6 – 10)	975	33.7	32.0 – 35.4	965	33.4	31.5 – 35.4

Supplementary Table 2 Predictors of participants with correct understanding of meningococcal disease severity*

Variable	Participants with a correct answer		Participants with an incorrect answer		Univariate Associations			Multivariate Logistic Regression Analysis		
					Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	95% CI	p-value
Age	**n**	**%**	**n**	**%**			**<0.001**			**0.002**
15 – 24	334	68.7	153	31.3	1.00	-		-		
25 – 54	1,365	91.0	136	9.0	4.60	3.27 – 6.47	<0.001	2.79	1.45 – 5.37	0.002
55+	962	90.3	103	9.7	4.27	3.07 – 5.93	<0.001	3.58	1.68 – 7.61	0.001
Gender	**n**	**%**	**n**	**%**						
Male	1,264	84.8	227	15.2	1.00	-		-		
Female	1,397	89.5	164	10.5	1.53	1.18 – 1.98	0.001	2.43	1.66 – 3.56	<0.001
Country of birth	**n**	**%**	**n**	**%**						
Non-Australia	584	74.2	203	25.8	1.00	-		-	-	
Australia	2,077	91.7	188	8.3	3.85	2.95 – 5.01	<0.001	3.82	2.64 – 5.53	<0.001
Marital Status	**n**	**%**	**n**	**%**						
Married/De Facto	1,748	91.9	154	8.1	1.00	-		-	-	
Single	910	79.4	237	20.6	0.34	0.26 – 0.44	<0.001	0.58	0.39 – 0.87	0.008
Educational attainment	**n**	**%**	**n**	**%**			**0.006**			**0.023**
Lower than Year 12 education	892	84.1	168	15.9	1.00	-		-	-	
Higher than or equal to Year 12 education/trade/ certificate/diploma	1,154	88.3	153	11.7	1.42	1.07 – 1.90	0.016	1.83	1.19 – 2.81	0.006
Degree or higher	613	90.0	68	10.0	1.70	1.18 – 2.45	0.004	1.51	0.87 – 2.61	0.144
Work status	**n**	**%**	**n**	**%**			**<0.001**			**0.068**
Employed	1,510	90.6	157	9.4	1.00	-		-	-	
Unemployed	262	87.4	38	12.6	0.72	0.47 – 1.12	0.147	0.68	0.34 – 1.35	0.271
Retired	538	87.8	75	12.2	0.75	0.55 – 1.00	0.055	0.79	0.39 – 1.61	0.519
Student	220	66.6	110	33.4	0.21	0.14 – 0.30	<0.001	0.73	0.33 – 1.59	0.425
Other	131	92.1	11	7.9	1.22	0.60 – 2.47	0.588	3.33	.07 – 10.37	0.038
Household income	**n**	**%**	**n**	**%**			**0.001**			**0.015**
Low (≤ AUD $40,000)	513	88.2	68	11.8	1.00	-		-	-	
Medium (AUD $40,001 – $80,000)	547	94.0	35	6.0	2.09	1.31 – 3.34	0.002	2.15	1.26 – 3.66	0.005
High (≥ AUD $80,001)	880	93.5	61	6.5	1.93	1.31 – 2.86	0.001	1.82	1.01 – 3.29	0.046
Area	**n**	**%**	**n**	**%**						
Metropolitan	1,923	86.1	310	13.9	1.00	-		-	-	
Regional	738	90.1	81	9.9	1.48	1.07 – 2.03	0.016	1.66	1.03 – 2.68	0.038
Socio-economic status	**n**	**%**	**n**	**%**			**0.520**			
Low (1st – 33rd percentile)	997	86.1	161	13.9	1.00	-		-	-	-
Medium (34th – 66th percentile)	799	88.0	108	12.0	1.19	0.87 – 1.63	0.290	-	-	-
High (67th – 100th percentile)	865	87.6	122	12.4	1.14	0.84 – 1.56	0.402	-	-	-
Participant's parental status	**n**	**%**	**n**	**%**						
No	1,787	86.0	291	14.0	1.00	-		-	-	
Yes	871	89.7	100	10.3	1.42	1.05 – 1.93	0.022	0.80	0.46 – 1.39	0.433

* All results were weighted.

Supplementary Table 3 Predictors of participants with correct understanding of meningococcal disease incidence*

Variable	Participants with a correct answer		Participants with an incorrect answer		Univariate Associations			Multivariate Logistic Regression Analysis		
					Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	95% CI	p-value
Age	**n**	**%**	**n**	**%**			**<0.001**			**0.034**
15 – 24	85	17.5	402	82.5	1.00	-		-	-	
25 – 54	508	33.9	992	66.1	2.42	1.75 – 3.35	<0.001	1.85	1.10 – 3.12	0.020
55+	334	31.4	732	68.6	2.16	1.56 – 2.99	<0.001	1.51	0.86 – 2.65	0.147
Gender	**n**	**%**	**n**	**%**						
Male	554	37.1	939	62.9	1.00	-		-	-	
Female	374	23.9	1,187	76.1	0.53	0.45 – 0.63	<0.001	0.48	0.39 – 0.59	<0.001
Country of birth	**n**	**%**	**n**	**%**						
Non-Australia	199	25.4	587	74.6	1.00	-		-	-	
Australia	728	32.1	1,539	67.9	1.39	1.14 – 1.70	0.001	1.37	1.08 – 1.74	0.010
Marital Status	**n**	**%**	**n**	**%**						
Married/De Facto	633	33.2	1,271	66.8	1.00	-		-	-	
Single	295	25.7	852	74.3	0.69	0.58 – 0.83	<0.001	1.18	0.93 – 1.48	0.169
Educational attainment	**n**	**%**	**n**	**%**			**<0.001**			**<0.001**
Lower than Year 12 education	270	25.4	792	74.6	1.00	-		-	-	
Higher than or equal to Year 12 education/trade/ certificate/diploma	368	28.2	939	71.8	1.15	0.94 – 1.41	0.175	0.93	0.72 – 1.20	0.585
Degree or higher	290	42.5	392	57.5	2.17	1.73 – 2.73	<0.001	1.57	1.17 – 2.13	0.003
Work status	**n**	**%**	**n**	**%**			**<0.001**			**0.407**
Employed	561	33.6	1,107	66.4	1.00	-		-	-	
Unemployed	67	22.5	231	77.5	0.57	0.42 – 0.79	0.001	0.90	060 – 1.34	0.601
Retired	187	30.5	426	69.5	0.87	0.71 – 1.05	0.150	1.28	0.91 – 1.80	1.157
Student	63	19.2	266	80.8	0.47	0.32 – 0.69	<0.001	0.71	0.37 – 1.39	0.322
Other	49	33.8	95	66.2	1.01	0.68 – 1.49	0.966	1.06	0.65 – 1.75	0.806
Household income	**n**	**%**	**n**	**%**			**<0.001**			**0.023**
Low (≤ AUD $40,000)	158	27.1	424	72.9	1.00	-		-	-	
Medium (AUD $40,001 – $80,000)	178	30.5	405	69.5	1.18	0.92 – 1.52	0.201	1.10	0.82 – 1.49	0.527
High (≥ AUD $80,001)	388	41.2	553	58.8	1.88	1.50 – 2.36	<0.001	1.51	1.09 – 2.11	0.014
Area	**n**	**%**	**n**	**%**						
Metropolitan	676	30.2	1,558	69.8	1.00	-		-	-	-
Regional	252	30.8	568	69.2	1.02	0.84 – 1.25	0.811	-	-	-
Socio-economic status	**n**	**%**	**n**	**%**			**<0.001**			**0.011**
Low (1st – 33rd percentile)	301	25.9	859	74.1	1.00	-		-	-	
Medium (34th – 66th percentile)	276	30.5	630	69.5	1.25	1.01 – 1.55	0.038	1.29	1.00 – 1.66	0.047
High (67th – 100th percentile)	351	35.5	637	64.5	1.57	1.28 – 1.93	<0.001	1.47	1.14 – 1.91	0.003
Participant's parental status	**n**	**%**	**n**	**%**						
No	634	30.5	1,445	69.5	1.00	-		-	-	-
Yes	294	30.2	677	69.8	0.99	0.82 – 1.20	0.900	-	-	-

* All results were weighted.

Supplementary Table 4 Predictors of participants with correct understanding of meningococcal disease susceptibility*

Variable	Participants with a correct answer		Participants with an incorrect answer		Univariate Associations			Multivariate Logistic Regression Analysis		
					Odds Ratio	95% CI	p-value	Adjusted Odds Ratio	95% CI	p-value
Age	**n**	**%**	**n**	**%**			**<0.001**			**0.399**
15 – 24	211	43.5	274	56.5	1.00	-		-	-	
25 – 54	871	58.1	629	41.9	1.80	1.37 – 2.36	<0.001	1.12	0.72 – 1.74	0.625
55+	606	56.9	459	43.1	1.71	1.31 – 2.25	<0.001	1.32	0.82 – 2.14	0.251
Gender	**n**	**%**	**n**	**%**						
Male	778	52.2	714	47.8	1.00	-		-	-	
Female	911	58.4	649	41.6	1.29	1.09 – 1.52	0.002	1.34	1.10 – 1.64	0.004
Country of birth	**n**	**%**	**n**	**%**						
Non-Australia	397	50.4	390	49.6	1.00	-		-	-	
Australia	1,292	57.1	972	42.9	1.31	1.09 – 1.57	0.004	1.11	0.89 – 1.40	0.344
Marital Status	**n**	**%**	**n**	**%**						
Married/De Facto	784	58.8	1,121	41.2	1.00	-		-	-	
Single	577	49.5	567	50.5	0.69	0.58 – 0.81	<0.001	0.94	0.76 – 1.18	0.614
Educational attainment	**n**	**%**	**n**	**%**			**<0.001**			**0.285**
Lower than Year 12 education	529	49.8	533	50.2	1.00	-		-	-	
Higher than or equal to Year 12 education/ trade/ certificate/diploma	733	56.2	571	43.8	1.29	1.08 – 1.55	0.006	1.14	0.90 – 1.44	0.265
Degree or higher	425	62.4	256	37.6	1.67	1.33 – 2.08	<0.001	1.26	0.94 – 1.69	0.122
Work status	**n**	**%**	**n**	**%**			**<0.001**			**0.200**
Employed	983	59.0	682	41.0	1.00	-		-	-	
Unemployed	162	54.1	137	45.9	0.82	0.62 – 1.09	0.165	0.91	0.64 – 1.30	0.606
Retired	340	55.5	272	44.5	0.87	0.72 – 1.04	0.132	1.13	0.82 – 1.57	0.444
Student	138	41.8	192	58.2	0.50	0.36 – 0.69	<0.001	0.71	0.39 – 1.28	0.255
Other	65	45.5	78	54.5	0.58	0.40 – 0.83	0.003	0.68	0.44 – 1.06	0.092
Household income	**n**	**%**	**n**	**%**			**0.010**			**0.156**
Low (≤ AUD $40,000)	319	54.8	263	45.2	1.00	-		-	-	
Medium (AUD $40,001 – $80,000)	346	59.4	236	40.6	1.21	0.95 – 1.53	0.120	1.22	0.93 – 1.60	0.157
High (≥ AUD $80,001)	592	63.0	348	37.0	1.40	1.13 – 1.74	0.002	1.35	0.99 – 1.84	0.057
Area	**n**	**%**	**n**	**%**						
Metropolitan	1,214	54.4	1,017	45.6	1.00	-		-	-	
Regional	475	57.9	345	42.1	1.15	0.96 – 1.39	0.132	1.44	1.13 – 1.82	0.003
Socio-economic status	**n**	**%**	**n**	**%**			**0.010**			**0.014**
Low (1st – 33rd percentile)	615	53.0	544	47.0	1.00	-		-	-	
Medium (34th – 66th percentile)	484	53.4	422	46.6	1.02	0.84 – 1.24	0.865	0.93	0.74 – 1.18	0.570
High (67th – 100th percentile)	590	59.8	396	40.2	1.32	1.08 – 1.61	0.006	1.35	1.03 – 1.76	0.027
Participant's parental status	**n**	**%**	**n**	**%**						
No	1,113	53.6	963	46.4	1.00	-		-	-	
Yes	572	58.9	399	41.1	1.24	1.04 – 1.48	0.019	1.23	0.94 – 1.60	0.124

* All results were weighted.

5.6 REFERENCES

1. Hart CA, Thomson AP. Meningococcal disease and its management in children. *BMJ (Clinical research ed).* 2006;333(7570):685-90.

2. Chiu C, Dey A, Wang H, Menzies R, Deeks S, Mahajan D, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2005 to 2007. *Commun Dis Intell.* 2010;34(Supplement):S50-6.

3. The Australian Immunisation Handbook 10th edition 2013, National Health Medical Research Council, Department of Health and Ageing, Canberra.

4. Annual report of the Australian Meningococcal Surveillance Programme, 2001. *Commun Dis Intell Q Rep.* 2002;26(3):407-18.

5. Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2011. *Commun Dis Intell Q Rep.* 2012;36(3):E251-62.

6. Novartis Media Relations. Novartis vaccine Bexsero® approved in Australia to help protect against MenB disease, a deadly form of bacterial meningitis. [updated 15 August 2013, accessed 07 October 2013]; Available from: http://www.novartis.com/newsroom/media-releases/en/2013/1723151.shtml.

7. UK. Department of Health. JCVI interim position statement on use of Bexsero® meningococcal B vaccine in the UK. [database on the Internet]. London: Department of Health; 2013 [cited 07 October 2013]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224896/JCVI_interim_statement_on_meningococcal_B_vaccination_for_web.pdf.

8. Black S. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):858.

9. Blewitt J. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):857-8.

10. Eskola J. Immunisation against meningococcus B. *Lancet*. 2013;382(9897):1019.

11. Finn A, Malley R. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):857.

12. Head C. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):935.

13. Lambert PH. Immunisation against meningococcus B. *Lancet.* 2013;382(9897):1019.

14. Plotkin SA. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):858.

15. Rappuoli R. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):935-6.

16. Taha M-K. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):936.

17. Moxon R, Snape MD. The price of prevention: What now for immunisation against meningococcus B? *Lancet.* 2013;382(9890):369-70.

18. *November 2013 PBAC Outcomes - 1st Time Decisions Not to Recommend*, Pharmaceutical Benefits Advisory Committee (PBAC), The Department of Health, Commenwealth of Australia, viewed 31 Jan 2014, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2013-11>

19. "Patients want "compassion" on meningococcal vaccine", *PharmaDispatch*, viewed 31 Jan 2014, <http://www.pharmadispatch.com/patients-want-compassion-on-meningococcal-vaccine/>

20. Snape MD, Medini D, Halperin SA, DeTora L, Drori J, Moxon ER. The challenge of post-implementation surveillance for novel meningococcal vaccines. *Vaccine*. 2012 30;30 Suppl 2:B67-72.

21. Noakes K, Yarwood J, Salisbury D. Parental response to the introduction of a vaccine against human papilloma virus. *Hum Vaccin*. 2006;2(6):243-8.

22. Ortiz JR, Neuzil KM, Ahonkhai VI, Gellin BG, Salisbury DM, Read JS, et al. Translating vaccine policy into action: a report from the Bill & Melinda Gates Foundation Consultation on the prevention of maternal and early infant influenza in resource-limited settings. *Vaccine*. 2012;30(50):7134-40

23. Yarwood J, Noakes K, Kennedy D, Campbell H, Salisbury D. Tracking mothers attitudes to childhood immunisation 1991-2001. *Vaccine.* 2005;23(48-49):5670-87.

24. Dorell C, Yankey D, Strasser S. Parent-reported reasons for nonreceipt of recommended adolescent vaccinations, national immunization survey: teen, 2009. *Clin Pediatr (Phila)*. 2011;50(12):1116-24.

25. Hak E, Schonbeck Y, De Melker H, Van Essen GA, Sanders EA. Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program. *Vaccine.* 2005;23(24):3103-7.

26. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine*. 2013;31(23):2638-46.

27. Bakhache P, Rodrigo C, Davie S, Ahuja A, Sudovar B, Crudup T, et al. Health care providers' and parents' attitudes toward administration of new infant vaccines--a multinational survey. *Eur J Pediatr*. 2013;172(4):485-92.

28. Petousis-Harris H, Turner N, Soe B. Parent views on school based immunisation: A survey of parents of year 1 and 6 in three diverse Auckland schools. *N Z Fam Physician.* 2004;31(4):222-8.

29. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Attitudes and risk perception of parents of different ethnic backgrounds regarding meningococcal C vaccination. *Vaccine.* 2005;23(25):3329-35.

30. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Parents' perceived vulnerability and perceived control in preventing Meningococcal C infection: a large-scale interview study about vaccination. *BMC Public Health*. 2008;8:45.

31. *Health Omnibus Survey Methodology Brief Report 2012,* Population Research and Outcomes Studies Unit, The University of Adelaide, Adelaide.

32. Pink B. Information paper: an introduction to socio-economic indexes for areas (SEIFA), 2006. Canberra: Australian Bureau of Statistics (ABS); 2008

33. Marshall H, Tooher R, Collins J, Mensah F, Braunack-Mayer A, Street J, et al. Awareness, anxiety, compliance: community perceptions and response to the threat and reality of an influenza pandemic. *Am J Infect Control.* 2012;40(3):270-2.

34. Marshall H, Ryan P, Roberton D, Baghurst P. A cross-sectional survey to assess community attitudes to introduction of Human papillomavirus vaccine. *Aust N Z J Public Health*. 2007;31(3):235-42.

35. Goodman E, Cohall AT. Acquired immunodeficiency syndrome and adolescents: knowledge, attitudes, beliefs, and behaviors in a New York City adolescent minority population. *Pediatrics*. 1989;84(1):36-42.

36. Robb KA, Miles A, Campbell J, Evans P, Wardle J. Can cancer risk information raise awareness without increasing anxiety? A randomized trial. *Prev Med.* 2006;43(3):187-90.

37. Flood EM, Rousculp MD, Ryan KJ, Beusterien KM, Divino VM, Toback SL, et al. Parents' decision-making regarding vaccinating their children against influenza: A web-based survey. *Clin Ther.* 2010;32(8):1448-67.

38. Eppes C, Wu A, You W, Cameron KA, Garcia P, Grobman W. Barriers to influenza vaccination among pregnant women. *Vaccine.* 2013;31(27):2874-8.

39. Bedford H, Lansley M. More vaccines for children? Parents' views. *Vaccine.* 2007;25(45):7818-23.

40. Pitman RJ, Nagy LD, Sculpher MJ. Cost-effectiveness of childhood influenza vaccination in England and Wales: Results from a dynamic transmission model. *Vaccine*. 2013;31(6):927-42.

Our study results can provide important information to policy makers and immunisation educators for developing community tailored educational programs so as to improve the general public's understanding and awareness of IMD. Improvement of public awareness of a vaccine-preventable disease would be essential to optimise uptake of a new MenB vaccine.

CHAPTER 6: CONCLUSION

6.1 CONCLUSION AND RESEARCH TRANSLATION

Our study results have provided invaluable insights into clinical outcomes, inpatient costs, hospital service use and community knowledge and awareness of IMD from a public health perspective. To the best of our knowledge, admission costs and adolescents' and non-parents' knowledge of and concern about IMD, have not previously been assessed in Australia. Clinical outcomes associated with IMD in Australian children have not been investigated in the post meningococcal C vaccine era.

With thorough review of hospital notes and long follow-up period for patients who developed sequelae (mean: 645.8 days), a high sequelae rate (37.6%) was reported in our study with two inpatient deaths. Our study shows strong evidence that presence of sequelae was not uncommon in children admitted to hospital with IMD and could have a profound long-term impact on individuals and their families. The Australian Technical Advisory Group on Immunisation (ATAGI) and the Meningitis Research Foundation in the UK have already requested and received a copy of our study publication regarding clinical outcomes, to inform future decisions for inclusion of the new MenB vaccine in childhood immunisation programs with delivery of useful information to other research groups. Three clinical factors were identified as independent predictors of sequelae, which may help clinical staff prioritise patient assessment and management and predicate clinical prognoses.

The new MenB vaccine has been approved in the EU and Australia for use in individuals two months of age and older to protect against meningococcal B infection.[1] However, an interim position statement from the UK Government's JCVI recommended the MenB vaccine to not be included in the UK funded routine immunisation program.[2] Considerable controversy surrounding their interim decision has been aroused among health professionals, advocates and research foundations,[3-11] which was acknowledged in an update of JCVI's statement.[12] The PBAC in Australia did not recommend the inclusion of the multicomponent meningococcal B vaccine on the National Immunisation Program Schedule mainly because of its unfavourable level of cost-effectiveness. [13] A resubmission is planned to clarify and address the issues raised by the PBAC.[14] Our costing study shows the inpatient costs of acute infection are significantly higher than an average hospital admission. Sequelae resulted in a significant increase in inpatient costs. Although the association between serogroup B infection and development of sequelae was not statistically significant, children with serogroup B IMD were more likely to have higher inpatient costs and readmission costs compared with non-serogroup B cases. Infants less than one year old have the highest incidence of IMD and had higher inpatient costs and readmission costs in our study. Our study results can not only be used in future economic evaluation of new meningococcal vaccines, but can also provide useful information such as the cost saving and the medical benefits to inform public funding decisions.

Adolescents are a target group for introduction of a MenB vaccine. However, no previous studies have investigated knowledge of and concern about IMD in adolescents. 3055 participants took part in our survey including adolescents,

parents and non-parents, providing detailed information on level of awareness and concern about IMD in each of these groups.[15-18] Our study demonstrates adolescents had lower knowledge than adults. Moreover, non-parental, male, single, highly educated or high household income participants were more likely to have lower concern about the disease. Our study results suggest tailored community educational programs may be preferable than developing a universal educational program.

Although IMD admissions during an eleven year period were reviewed, the sample size is still small (n=109). All IMD cases were from a single tertiary centre and, thus, possibly not generally representative of all cases in Australia. As clinical outcome and costing components of this project are based on a retrospective audit study, imperfect hospital records, missing data due to loss to follow-up, and lack of indirect costs caused by productivity loss are limitations of our study. A multicentre prospective study is needed to comprehensively assess clinical and economic burden of IMD. Our survey results are generalisable as we surveyed randomly selected households with all results weighted to the population level.

Decisions regarding inclusion of a new vaccine are not only based on cost-effectiveness and incidence, but also on a range of other factors including vaccine safety, long-term impact and costs. Our study investigated clinical outcomes, inpatient costs and hospital service use following IMD, and assessed community knowledge of and concern about the disease, which could assist greatly in informing public health decisions of a new meningococcal vaccination initiative.

6.2 REFERENCES

1. Novartis Media Relations. Novartis vaccine Bexsero® approved in Australia to help protect against MenB disease, a deadly form of bacterial meningitis. [updated 15 August 2013; accessed 07 October 2013]; Available from: http://www.novartis.com/newsroom/media-releases/en/2013/1723151.shtml.

2. Joint Committee on Vaccination and Immunisation (JCVI) interim position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health; 2013 [updated 24 July 2013; accessed 2 September 2013]; Available from: https://www.gov.uk/government/publications/jcvi-interim-position-statement-on-the-use-of-bexsero-meningococcal-b-vaccine-in-the-uk.

3. Black S. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):858.

4. Blewitt J. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):857-8.

5. Eskola J. Immunisation against meningococcus B. *Lancet.* 2013;382(9897):1019.

6. Finn A, Malley R. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):857.

7. Head C. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):935.

8. Lambert PH. Immunisation against meningococcus B. *Lancet.* 2013;382(9897):1019.

9. Plotkin SA. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):858.

10. Rappuoli R. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):935-6.

11. Taha M-K. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):936.

12. Update on the outcome of consultation about use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health; 2013 [updated 25 October 2013; accessed 20 November 2013]; Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/252859/JCVI_MenB_Update.pdf.

13. *November 2013 PBAC Outcomes - 1st Time Decisions Not to Recommend*, Pharmaceutical Benefits Advisory Committee (PBAC), The Department of Health, Commenwealth of Australia, viewed 31 Jan 2014, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2013-11>

14. "Patients want "compassion" on meningococcal vaccine", *PharmaDispatch*, viewed 31 Jan 2014, <http://www.pharmadispatch.com/patients-want-compassion-on-meningococcal-vaccine/>

15. Hak E, Schonbeck Y, De Melker H, Van Essen GA, Sanders EA. Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program. *Vaccine.* 2005;23(24):3103-7.

16. Petousis-Harris H, Turner N, Soe B. Parent views on school based immunisation: A survey of parents of year 1 and 6 in three diverse Auckland schools. *N Z Fam Physician*. 2004;31(4):222-8.

17. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Attitudes and risk perception of parents of different ethnic backgrounds regarding meningococcal C vaccination. *Vaccine.* 2005;23(25):3329-35.

18. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Parents' perceived vulnerability and perceived control in preventing Meningococcal C infection: a large-scale interview study about vaccination. *BMC Public Health*. 2008;8:45.

BIBLIOGRAPHY

6401.0 Consumer Price Index, Australia. TABLE 11. CPI: Group, Sub-group and Expenditure Class, Index Numbers by Capital City. Australian Bureau of Statistics; 2012 [accessed 12 Jan 2013]; Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/6401.0Sep%202012.

Al-Tawfiq JA, Clark TA, Memish ZA. Meningococcal disease: the organism, clinical presentation, and worldwide epidemiology. *J Travel Med*. 2010;17 Suppl:3-8.

Annual report of the Australian Meningococcal Surveillance Programme, 2001. *Commun Dis Intell*. 2002;26(3):407-18.

Annual report of the Australian Meningococcal Surveillance Programme, 2002. *Commun Dis Intell*. 2003;27(2):196-208.

Annual report of the Australian Meningococcal Surveillance Programme, 2009. *Commun Dis Intell.* 2010 Sep;34(3):291-302.

Australian Meningococcal Surveillance Programme annual report, 2010. *Commun Dis Intell.* 2011 Sep;35(3):217-28.

Atkinson W. Epidemiology and prevention of vaccine-preventable diseases: Dept. of Health & Human Services, Public Health Service, Centers for Disease Control and Prevention; 2000.

Guidelines for the Early Clinical and Public Health Management of Meningococcal Disease in Australia 2007, Communicable Diseases Network Australia (CDNA), Department of Health and Ageing, Canberra.

The Australian Immunisation Handbook 10th edition 2013, 2013, National Health Medical Research, Department of Health and Aging, Canberra.

Health Omnibus Survey Methodology Brief Report 2012, Population Research and Outcomes Studies Unit, The University of Adelaide.

Bakhache P, Rodrigo C, Davie S, Ahuja A, Sudovar B, Crudup T, et al. Health care providers' and parents' attitudes toward administration of new infant vaccines--a multinational survey. *Eur J Pediatr*. 2013;172(4):485-92.

Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J*. 1993;12(5):389-94.

Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Serv Res Policy*. 2004;9(4):197-204.

Basu A, Manning WG. Issues for the next generation of health care cost analyses. *Med Care*. 2009;47(7 Suppl 1):S109-14.

Bedford H, Lansley M. More vaccines for children? Parents' views. *Vaccine*. 2007;25(45):7818-23.

Beeson PB, Westerman E. Cerebrospinal Fever and Sulphonamides. *Br Med J*. 1943;1(4294):497-500.

Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The disease burden of invasive meningococcal serogroup B disease in Canada. *Pediatr Infect Dis J*. 2013;32(1):e20-5.

Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The impact of childhood meningococcal serogroup C conjugate vaccine programs in Canada. *Pediatr Infect Dis J*. 2009;28(3):220-4.

Bilukha OO, Rosenstein N. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and Reports*. 2005 May;54(RR-7):1-21.

Bjune G. "Herd immunity" and the meningococcal vaccine trial in Norway. *Lancet.* 1992;340(8814):315.

Black S. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):858.

Blewitt J. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):857-8.

Boisier P, Nicolas P, Djibo S, Taha MK, Jeanne I, Mainassara HB, et al. Meningococcal meningitis: unprecedented incidence of serogroup X-related cases in 2006 in Niger. *Clin Infect Dis*. 2007;44(5):657-63.

Booy R, Richmond P, Nolan T, et al. Three-year antibody persistence and safety after a single dose of combined haemophilus influenzae type b (Hib)-Neisseria meningitidis serogroup C-tetanus toxoid conjugate vaccine in Hib-primed toddlers. *Pediatr Infect Dis J.* 2013;32(2):169-74.

Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. *Pediatrics*. 2009;123(3):e502-9.

Boslego J, Garcia J, Cruz C, Zollinger W, Brandt B, Ruiz S, et al. Efficacy, safety, and immunogenicity of a meningococcal group B (15:P1.3) outer membrane protein vaccine in Iquique, Chile. Chilean National Committee for Meningococcal Disease. *Vaccine.* 1995;13(9):821-9.

Brandtzaeg P, Mollnes TE, Kierulf P. Complement activation and endotoxin levels in systemic meningococcal disease. *J Infect Dis*. 1989;160(1):58-65.

Campsall PA, Laupland KB, Niven DJ. Severe meningococcal infection: a review of epidemiology, diagnosis, and management. *Crit Care Clin*. 2013;29(3):393-409.

Carter NJ. Multicomponent meningococcal serogroup B vaccine (4CMenB; Bexsero®): a review of its use in primary and booster vaccination. *BioDrugs.* 2013;27(3):263-74.

Cartwright KA. Early management of meningococcal disease. *Infect Dis Clin North Am*. 1999;13(3):661-84, viii.

Causes of death Australia 2007. Australian Bureau of Statistics; 2009 [Accessed 12 December 2012]; Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3303.02009?OpenDocument.

Chiu C, Dey A, Wang H, Menzies R, Deeks S, Mahajan D, et al. Vaccine preventable diseases in Australia, 2005 to 2007. *Commun Dis Intell*. 2010;34 Suppl:S50-6.

Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine*. 2013;31(23):2638-46.

Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(12):853-61.

Cohn AC, Harrison LH. Meningococcal vaccines: current issues and future strategies. *Drugs*. 2013;73(11):1147-55.

Cohn AC, MacNeil JR, Harrison LH, Hatcher C, Theodore J, Schmidt M, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998-2007: implications for prevention of meningococcal disease. *Clin Infect Dis*. 2010;50(2):184-91.

Dang V, Jamieson FB, Wilson S, Rawte P, Crowcroft NS, Johnson K, et al. Epidemiology of serogroup B invasive meningococcal disease in Ontario, Canada, 2000 to 2010. *BMC Infect Dis.* 2012;12:202.

Davis KL, Bell TJ, Miller JM, Misurski DA, Bapat B. Hospital costs, length of stay and mortality associated with childhood, adolescent and young adult meningococcal disease in the US. *Appl Health Econ Health Policy*. 2011;9(3):197-207.

Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. *Hum Vaccin*. 2011;7(4):458-65.

Davis KL, Misurski DA, Miller JM, Bell TJ, Bapat B. Cost of acute hospitalization and post-discharge follow-up care for meningococcal disease in the United States. *Hum Vaccin*. 2011;7(1):96-101.

Davison AC. Bootstrap methods and their application. Cambridge: Cambridge University Press; 1997.

Djupesland G, Gedde-Dahl TW. Sequelae of meningococcal disease - studied about six weeks after hospital admission. *NIPH Ann*. 1983;6(1):85-90.

Dorell C, Yankey D, Strasser S. Parent-reported reasons for nonreceipt of recommended adolescent vaccinations, national immunization survey: teen, 2009. *Clin Pediatr (Phila)*. 2011;50(12):1116-24.

Durand-Zaleski I. Why cost-of-illness studies are important and inform policy. *Vasc Med.* 2008;13(3):251-3.

Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(5):317-28.

Edwards MS, Baker CJ. Complications and sequelae of meningococcal infections in children. *J Pediatr.* 1981;99(4):540-5.

Eppes C, Wu A, You W, Cameron KA, Garcia P, Grobman W. Barriers to influenza vaccination among pregnant women. *Vaccine*. 2013;31(27):2874-8.

Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec, Canada, 1990-1994. *Clin Infect Dis*. 1998 May;26(5):1159-64.

Eskola J. Immunisation against meningococcus B. *Lancet*. 2013;382(9897):1019.

Finn A, Malley R. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):857.

Finne J, Leinonen M, Makela PH. Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine development and pathogenesis. *Lancet.* 1983;2(8346):355-7.

Fischer M, Hedberg K, Cardosi P, Plikaytis BD, Hoesly FC, Steingart KR, et al. Tobacco smoke as a risk factor for meningococcal disease. *Pediatr Infect Dis J.* 1997;16(10):979-83.

Flood EM, Rousculp MD, Ryan KJ, Beusterien KM, Divino VM, Toback SL, et al. Parents' decision-making regarding vaccinating their children against influenza: A web-based survey. *Clin Ther*. 2010;32(8):1448-67.

Frosch M, Maiden MCJ. Handbook of meningococcal disease. Wiley Online Library; 2006.

Getsios D, Caro I, El-Hadi W, Caro JJ. Assessing the economics of vaccination for Neisseria meningitidis in industrialized nations: a review and recommendations for further research. *Int J Technol Assess Health Care*. 2004;20(3):280-8.

Gilca R, Deceuninck G, Lefebvre B, Tsang R, Amini R, Gilca V, et al. The changing epidemiology of meningococcal disease in Quebec, Canada, 1991-2011: potential implications of emergence of new strains. *PloS one.* 2012;7(11):e50659.

Gilmore A, Stuart J, Andrews N. Risk of secondary meningococcal disease in health-care workers. *Lancet*. 2000;356(9242):1654-5.

Girard MP, Preziosi MP, Aguado MT, Kieny MP. A review of vaccine research and development: meningococcal disease. *Vaccine.* 2006;24(22):4692-700.

Gold R. Clinical aspects of meningococcal disease. In: Evolution of meningococcal disease. Volume 11. 1987. Pp: 69–97. Boca Raton, Florida: CRC Press.

Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005 Jan;6(1):2-8.

Goldstein B, Giroir B, Randolph A. Reply: Values for Systolic Blood Pressure. *Pediatr Crit Care Med*. 2005;6(4):500-1.

Goodman E, Cohall AT. Acquired immunodeficiency syndrome and adolescents: knowledge, attitudes, beliefs, and behaviors in a New York City adolescent minority population. *Pediatrics*. 1989;84(1):36-42.

Gottfredsson M, Reynisson IK, Ingvarsson RF, Kristjansdottir H, Nardini MV, Sigurdsson JF, et al. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. *Clin Infect Dis.* 2011;53(9):e117-24.

Granoff DM, Pelton S, Harrison LH. Meningococcal vaccines. *Vaccines*: *Expert Consult-Online*. 2012:388.

Griffiths UK, Dieye Y, Fleming J, Hajjeh R, Edmond K. Costs of meningitis sequelae in children in Dakar, Senegal. *Pediatr Infect Dis J*. 2012;31(11):e189-95.

Grimwood K, Anderson VA, Bond L, Catroppa C, Hore RL, Keir EH, et al. Adverse outcomes of bacterial meningitis in school-age survivors. *Pediatrics*. 1995;95(5):646-56.

Guidelines for the early clinical and public health management of meningococcal disease in Australia 2007. Communicable Diseases Network Australia, Department of Health and Ageing, Canberra.

Guimont C, Hullick C, Durrheim D, Ryan N, Ferguson J, Massey P. Invasive meningococcal disease--improving management through structured review of cases in the Hunter New England area, Australia. *J Public Health (Oxf)*. 2010;32(1):38-43.

Hahne SJ, Charlett A, Purcell B, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ.* 2006 Jun;332(7553):1299-303.

Hak E, Schonbeck Y, De Melker H, Van Essen GA, Sanders EA. Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program. *Vaccine*. 2005;23(24):3103-7.

Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, et al. The changing and dynamic epidemiology of meningococcal disease. *Vaccine*. 2012;30 Suppl 2:B26-36.

Hanna J, McCall B, Murphy D. Invasive meningococcal disease in north Queensland, 1990-1994. *Commun Dis Intell.* 1996;20:320-4.

Hansman D. Meningococcal disease in South Australia: incidence and serogroup distribution 1971-1980. *J Hyg (Lond).* 1983 Feb;90(1):49-54.

Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine*. 2009;27 Suppl 2:B51-63.

Harrison LH. Epidemiological profile of meningococcal disease in the United States. *Clin Infect Dis.* 2010;50 Suppl 2:S37-44.

Hart CA, Thomson AP. Meningococcal disease and its management in children. *BMJ (Clinical research ed*). 2006;333(7570):685-90.

Head C. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):935.

Healy CM, Butler KM, Smith EO, Hensey OP, Bate T, Moloney AC, et al. Influence of serogroup on the presentation, course, and outcome of invasive meningococcal disease in children in the Republic of Ireland, 1995-2000. *Clin Infect Dis.* 2002;34(10):1323-30.

Hosmer DW, Lemeshow S: *Applied Logistic Regression.* 2nd ed. New York: Wiley; 2000.

Hospital performance: cost per casemix-adjusted separation. Australian Institute of Health and Welfare 2013; 2013 [Accessed 16 July 2013]; Available from: http://www.aihw.gov.au/haag10-11/hospital-performance-cost/.

Jelfs J, Munro R. Epidemiology of meningococcal disease in Australia. *J Paediatr Child Health*. 2001;37(5):S3-6.

Joint Committee on Vaccination and Immunisation (JCVI) interim position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health; 2013 [updated 24 July 2013; accessed 2 September 2013]; Available from: https://www.gov.uk/government/publications/jcvi-interim-position-statement-on-the-use-of-bexsero-meningococcal-b-vaccine-in-the-uk.

Jones D. Epidemiology of meningococcal disease in Europe and the USA. In: Cartwright K, editor. *Meningococcal disease.* Chichester: John Wiley & Sons; 1995. p. 147-57.

Jubb AA. Chemotherapy and Serotherapy in Cerebrospinal Meningitis. *Br Med J.* 1943;1(4294):501-4.

Karve S, Misurski D, Miller J, Davis KL. Costs of Sequelae Associated with Invasive Meningococcal Disease: Findings from a US Managed Care Population. *Health Outcomes Res Med*. 2011;2:e215-e226.

Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. *Pediatr Infect Dis J*. 1996 Nov;15(11):967-79.

Kliegman R. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, Pa: Saunders;2011:chap 184.

Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2011. *Commun Dis Intell*. 2012 Sep;36(3):E251-62.

Lambert PH. Immunisation against meningococcus B. *Lancet.* 2013;382(9897):1019.

Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. *Pharmacoeconomics.* 2011;29(8):653-71.

Maiden MC, Stuart JM, Group UKMC. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. *Lancet*. 2002;359(9320):1829-31.

Marshall H, Ryan P, Roberton D, Baghurst P. A cross-sectional survey to assess community attitudes to introduction of Human papillomavirus vaccine. *Aust N Z J Public Health*. 2007;31(3):235-42.

Marshall H, Tooher R, Collins J, Mensah F, Braunack-Mayer A, Street J, et al. Awareness, anxiety, compliance: community perceptions and response to the threat and reality of an influenza pandemic. *Am J Infect Control.* 2012;40(3):270-2.

Marshall HS, Richmond PC, Nissen MD, Jiang Q, Anderson AS, Jansen KU, et al. Safety and immunogenicity of a meningococcal B bivalent rLP2086 vaccine in healthy toddlers aged 18-36 months: a phase 1 randomized-controlled clinical trial. *Pediatr Infect Dis J*. 2012;31(10):1061-8.

Marshall HS, Richmond PC, Nissen MD, Wouters A, Baber J, Jiang Q, et al. A phase 2 open-label safety and immunogenicity study of a meningococcal B bivalent rLP2086 vaccine in healthy adults. *Vaccine.* 2013;31(12):1569-75.

Massey P, Durrheim D. Aboriginal and Torres Strait Islander peoples at higher risk of invasive meningococcal disease in NSW. *New South Wales Public Health Bulletin.* 2008;19(6):100-3.

Meningococcal disease prevention and control strategies for practice-based physicians (Addendum: recommendations for college students). Committee on Infectious Diseases. *Pediatrics*. 2000;106(6):1500-4.

Mercier JC, Beaufils F, Hartmann JF, Azema D. Hemodynamic patterns of meningococcal shock in children. *Crit Care Med.* 1988;16(1):27-33.

Miller MA, Shahab CK. Review of the cost effectiveness of immunisation strategies for the control of epidemic meningococcal meningitis. *Pharmacoeconomics.* 2005;23(4):333-43.

Monsell F. The skeletal consequences of meningococcal septicaemia. *Arch Dis Child.* 2012;97(6):539-44.

Moore PS. Meningococcal meningitis in sub-Saharan Africa: a model for the epidemic process. *Clin Infect Dis* 1992;14(2):515-25.

Moxon R, Snape MD. The price of prevention: What now for immunisation against meningococcus B? *Lancet.* 2013;382(9890):369-70.

Nissen MD, Marshall HS, Richmond PC, Jiang Q, Harris SL, Jones TR, et al. A randomized, controlled, phase 1/2 trial of a Neisseria meningitidis serogroup B bivalent rLP2086 vaccine in healthy children and adolescents. *Pediatr Infect Dis J.* 2013;32(4):364-71.

Noakes K, Yarwood J, Salisbury D. Parental response to the introduction of a vaccine against human papilloma virus. *Hum Vaccin*. 2006;2(6):243-8.

Notification Rate of Meningococcal disease (invasive)*, received from State and Territory health authorities in the period of 1991 to 2012 and year-to-date notifications for 2013 [database on the Internet]. Department of Health and Ageing [cited 8 November 2013]. Available from: http://www9.health.gov.au/cda/source/rpt_4.cfm.

Notification Rate of Meningococcal disease (invasive), Australia, 2012 by age group and sex [database on the Internet]. Department of Health and Ageing [accessed 23 July 2013]. Available from: http://www9.health.gov.au/cda/source/rpt_5.cfm.

Novartis Media Relations. Novartis vaccine Bexsero® approved in Australia to help protect against MenB disease, a deadly form of bacterial meningitis. [updated 15 August 2013; accessed 07 October 2013]; Available from: http://www.novartis.com/newsroom/media-releases/en/2013/1723151.shtml.

November 2013 PBAC Outcomes - 1st Time Decisions Not to Recommend, Pharmaceutical Benefits Advisory Committee (PBAC), The Department of Health, Commenwealth of Australia, viewed 31 Jan 2014, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2013-11>

Number of notifications of Meningococcal disease (invasive)*, received from State and Territory health authorities in the period of 1991 to 2012 and year-to-date notifications for 2013 [database on the Internet]. Department of Health and Ageing [cited 8 November 2013]. Available from: http://www9.health.gov.au/cda/source/rpt_4.cfm.

Number of notifications of Meningococcal disease (invasive), Australia, 2012 by age group and sex. Department of Health and Ageing; 2012 [Accessed 23 January 2013]; Available from: http://www9.health.gov.au/cda/Source/Rpt_5.cfm.

Number of notifications of Meningococcal disease (invasive), Australia, in the period of 1991 to 2011 and year-to-date notifications for 2012. [Department of Health and Ageing web site]. August 2012. Available from: http://www9.health.gov.au/cda/Source/Rpt_3.cfm. Accessed 15 August, 2012.

O'Brien JA, Caro JJ, Getsios D. Managing meningococcal disease in the United States: Hospital case characteristics and costs by age. *Value Health*. 2006;9(4):236-43.

Ogilvie G, Anderson M, Marra F, McNeil S, Pielak K, Dawar M, et al. A population-based evaluation of a publicly funded, school-based HPV vaccine program in British Columbia, Canada: parental factors associated with HPV vaccine receipt. *PLoS Med*. 2010;7(5):e1000270.

Olesch CA, Knight GJ. Invasive meningococcal infection in Western Australia. *J Paediatr Child Health.* 1999 Feb;35(1):42-8.

Ortiz JR, Neuzil KM, Ahonkhai VI, Gellin BG, Salisbury DM, Read JS, et al. Translating vaccine policy into action: a report from the Bill & Melinda Gates Foundation Consultation on the prevention of maternal and early infant influenza in resource-limited settings. *Vaccine*. 2012;30(50):7134-40

Ortega-Sanchez IR, Meltzer MI, Shepard C, Zell E, Messonnier ML, Bilukha O, et al. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. *Clin Infect Dis.* 2008;46(1):1-13.

Pace D, Pollard AJ. Meningococcal disease: clinical presentation and sequelae. *Vaccine*. 2012;30 Suppl 2:B3-9.

Pathan N, Faust SN, Levin M. Pathophysiology of meningococcal meningitis and septicaemia. *Arch Dis Child*. 2003;88(7):601-7.

"Patients want "compassion" on meningococcal vaccine", *PharmaDispatch*, viewed 31 Jan 2014, <http://www.pharmadispatch.com/patients-want-compassion-on-meningococcal-vaccine/>

Peltola H. Meningococcal disease: still with us. *Rev Infect Dis.* 1983;5(1):71-91.

Perkins BA, Jonsdottir K, Briem H, Griffiths E, Plikaytis BD, Hoiby EA, et al. Immunogenicity of two efficacious outer membrane protein-based serogroup B meningococcal vaccines among young adults in Iceland. *J Infect Dis.* 1998;177(3):683-91.

Pether JV, Lightfoot NF, Scott RJ, Morgan J, Steele-Perkins AP, Sheard SC. Carriage of Neisseria meningitidis: investigations in a military establishment. *Epidemiol Infect*. 1988;101(1):21-42.

Petousis-Harris H, Turner N, Soe B. Parent views on school based immunisation: A survey of parents of year 1 and 6 in three diverse Auckland schools. *N Z Fam Physician.* 2004;31(4):222-8.

Pink B. Information paper: an introduction to socio-economic indexes for areas (SEIFA), 2006. Canberra: Australian Bureau of Statistics (ABS); 2008

Pitman RJ, Nagy LD, Sculpher MJ. Cost-effectiveness of childhood influenza vaccination in England and Wales: Results from a dynamic transmission model. *Vaccine*. 2013;31(6):927-42.

Plotkin SA. Immunisation against meningococcus B. *Lancet.* 2013;382(9895):858.

Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. *N Engl J Med*. 1990;323(24):1651-7.

Ramakrishnan M, Ulland AJ, Steinhardt LC, Moisi JC, Were F, Levine OS. Sequelae due to bacterial meningitis among African children: a systematic literature review. *BMC Med*. 2009;7:47.

Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. *Lancet*. 2001;357(9251):195-6.

Rappuoli R. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):935-6.

Richmond PC, Marshall HS, Nissen MD, Jiang Q, Jansen KU, Garces-Sanchez M, et al. Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomised, single-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis*. 2012;12(8):597-607.

Richmond PC, Nissen MD, Marshall HS, Lambert SB, Roberton D, Gruber WC, et al. A bivalent Neisseria meningitidis recombinant lipidated factor H binding protein vaccine in young adults: results of a randomised, controlled, dose-escalation phase 1 trial. *Vaccine*. 2012;30(43):6163-74.

Robb KA, Miles A, Campbell J, Evans P, Wardle J. Can cancer risk information raise awareness without increasing anxiety? A randomized trial. *Prev Med.* 2006;43(3):187-90.

Roed C, Omland LH, Engsig FN, Skinhoj P, Obel N. Long-term mortality in patients diagnosed with meningococcal disease: a Danish nationwide cohort study. *PloS one.* 2010;5(3):e9662.

Rosenstein NE, Perkins BA, Stephens DS, Lefkowitz L, Cartter ML, Danila R, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. *J Infect Dis*. 1999;180(6):1894-901.

Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. *N Engl J Med*. 2001;344(18):1378-88.

Sander J, Bay D, Gedde-Dahl TW, et al. Late sequelae after meningococcal disease. A controlled study in young men. *NIPH Ann.* 1984 Jun;7(1):3-11.

Schildkamp RL, Lodder MC, Bijlmer HA, Dankert J, Scholten RJ. Clinical manifestations and course of meningococcal disease in 562 patients. *Scand J Infect Dis.* 1996;28(1):47-51.

Schoenbach EB, Phair JJ. The sensitivity of meningococci to sulfadiazine. *Am J Hyg*. 1948;47(2):177-86.

Schuchat A, Robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL, et al. Bacterial meningitis in the United States in 1995. *N Engl J Med.* 1997;337(14):970-6.

Scott RD, 2nd, Meltzer MI, Erickson LJ, De Wals P, Rosenstein NE. Vaccinating first-year college students living in dormitories for Meningococcal disease: an economic analysis. *Am J Prev Med*. 2002;23(2):98-105.

Shepard CW, Ortega-Sanchez IR, Scott Ii RD, Rosenstein NE. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. *Pediatrics*. 2005;115(5):1220-32.

Skull SA, Butler JR. Meningococcal vaccination for adolescents? An economic evaluation in Victoria. *J Paediatr Child Health*. 2001;37(5):S28-33.

Snape MD, Medini D, Halperin SA, DeTora L, Drori J, Moxon ER. The challenge of post-implementation surveillance for novel meningococcal vaccines. *Vaccine*. 2012 30;30 Suppl 2:B67-72.

Stephens DS. Biology and pathogenesis of the evolutionarily successful, obligate human bacterium Neisseria meningitidis. *Vaccine*. 2009;27 Suppl 2:B71-7.

Strelow VL, Vidal JE. Invasive meningococcal disease. *Arq Neuropsiquiatr*. 2013;71(9B):653-8.

Stuart JM, Cartwright KA, Robinson PM, Noah ND. Effect of smoking on meningococcal carriage. *Lancet.* 1989;2(8665):723-5.

Taha M-K. Immunisation against meningococcus B. *Lancet.* 2013;382(9896):936.

Tappero JW, Reporter R, Wenger JD, Ward BA, Reeves MW, Missbach TS, et al. Meningococcal disease in Los Angeles County, California, and among men in the county jails. *N Engl J Med*. 1996;335(12):833-40.

The Australian Immunisation Handbook 2013, National Health Medical Research Council, Department of Health and Ageing, Canberra.

Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Attitudes and risk perception of parents of different ethnic backgrounds regarding meningococcal C vaccination. *Vaccine*. 2005;23(25):3329-35.

Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Parents' perceived vulnerability and perceived control in preventing Meningococcal C infection: a large-scale interview study about vaccination. *BMC Public Health*. 2008;8:45.

Trotter CL, Chandra M, Cano R, et al. A surveillance network for meningococcal disease in Europe. *FEMS Microbiology Reviews.* 2007 Jan;31(1):27-36.

Trotter CL, Edmunds WJ. Modelling cost effectiveness of meningococcal serogroup C conjugate vaccination campaign in England and Wales. *BMJ (Clinical research ed).* 2002;324(7341):809.

Trotter CL, Edmunds WJ. Reassessing the cost-effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model. *Med Decis Making.* 2006;26(1):38-47.

Tsai CM, Frasch CE, Mocca LF. Five structural classes of major outer membrane proteins in Neisseria meningitidis. *J Bacteriol*. 1981;146(1):69-78.

Tully J, Viner RM, Coen PG, Stuart JM, Zambon M, Peckham C, et al. Risk and protective factors for meningococcal disease in adolescents: matched cohort study. *BMJ (Clinical research ed)*. 2006;332(7539):445-50.

UK. Department of Health. JCVI interim position statement on use of Bexsero® meningococcal B vaccine in the UK. [database on the Internet]. London: Department of Health; 2013 [cited 07 October 2013]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224896/JCVI_interim_statement_on_meningococcal_B_vaccination_for_web.pdf.

Update on the outcome of consultation about use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health; 2013 [updated 25 October 2013;

accessed 20 November 2013]; Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/252859/JCVI_MenB_Update.pdf.

van Deuren M, Brandtzaeg P, van der Meer JW. Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clin Microbiol Rev*. 2000;13(1):144-66.

Vieusseux M. Mémoire sur la maladie qui a régné à Genève au printemps de 1805. *J Med Chir Pharm*. 1805;11:163–182

Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. *Lancet Neurol*. 2012;11(9):774-83.

Visintin C, Mugglestone MA, Fields EJ, Jacklin P, Murphy MS, Pollard AJ, et al. Management of bacterial meningitis and meningococcal septicaemia in children and young people: summary of NICE guidance. *BMJ (Clinical research ed).* 2010;340:c3209.

Weichselbaum A. Ueber die Aetiologie der akuten Meningitis cerebro-spinalis. *Fortschr Med.* 1887; 5:573-583.

Wilder-Smith A, Barkham TM, Earnest A, Paton NI. Acquisition of W135 meningococcal carriage in Hajj pilgrims and transmission to household contacts: prospective study. *BMJ (Clinical research ed)*. 2002;325(7360):365-6.

World Health O. Dollars, DALYs and decisions: economic aspects of the mental health system. Geneva: World Health Organization. 2006.

Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease : scenarios of severe meningitis and septicemia. Paediatr Drugs. 2013;15(1):49-58.

Yarwood J, Noakes K, Kennedy D, Campbell H, Salisbury D. Tracking mothers attitudes to childhood immunisation 1991-2001. *Vaccine*. 2005;23(48-49):5670-87.

Zwahlen A, Nydegger UE, Vaudaux P, Lambert PH, Waldvogel FA. Complement-mediated opsonic activity in normal and infected human cerebrospinal fluid: early response during bacterial meningitis. *J Infect Dis*. 1982;145(5):635-46.

APPENDIX 1: BRIEF REPORT OF THE CLINICAL BURDEN AND PREDICTORS OF SEQUELAE FOLLOWING INVASIVE MENINGOCOCCAL DISEASE IN AUSTRALIAN CHILDREN

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The Clinical Burden and Predictors of Sequelae Following Invasive Meningococcal Disease in Australian Children

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Key Words: invasive meningococcal disease, sequelae

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APPENDIX 2: COMMUNITY, PARENTAL AND ADOLESCENT AWARENESS AND KNOWLEDGE OF MENINGOCOCCAL DISEASE (ACCEPTED BY THE JOURNAL "VACCINE")

Date: 2014/02/12

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Title: Community, parental and adolescent awareness and knowledge of meningococcal disease
Vaccine

Dear Ms. Bing Wang,

I am pleased to confirm that your paper "Community, parental and adolescent awareness and knowledge of meningococcal disease" has been accepted for publication in Vaccine. Comments from the Editor and Reviewers can be found below.

Now that you have had your paper accepted for publication in Vaccine, the editors of the journal invite you to make your contribution to the vital review process. If you have not yet done so, you can become a 'Reviewer' for Vaccine by contacting the support department at support@elsevier.com

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Thank you for submitting your work to Vaccine.

With kind regards,

Gregory A. Poland, M.D.
Editor In Chief
Vaccine

Comments from Editors and Reviewers:

HIGHLIGHTS

- Almost a quarter of participants had no knowledge of Invasive Meningococcal Disease.
- Adolescents had significantly lower knowledge of meningococcal disease compared to older adults.
- Being born in Australia, having a tertiary education, high household income, rural residential area and high socio-economic status were associated with higher knowledge of meningococcal disease.
- Participants, who were not parents, male gender, single, highly educated or had high household income, were more likely to have lower concern about meningococcal disease.

Title page

Title: Community, parental and adolescent awareness and knowledge of meningococcal disease

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ABSTRACT (word count 261)

Objective: To assess knowledge of invasive meningococcal disease (IMD) and concern about the disease in the South Australian Community including adolescents, adults, parents and non-parents.

Methods: This cross-sectional study was conducted by face to face interviews in South Australia in 2012. Participants were scored on their knowledge and concern about IMD. Univariate and multivariate regression analyses were performed with the survey data weighted by age and gender in accordance with 2011 Census data.

Results: Of 5,200 households randomly selected and stratified by metropolitan or rural location, 3,055 participants were interviewed with a response rate of 60.3%. The majority were Australian born (74.2%, n=2,267) with 31.8% (n=972) of those interviewed being parents, and 15.9% (n=487) adolescents (15 – 24 years). Almost a quarter of participants (23.5%, n=717) do not know what meningococcal disease is, with 9.1% (n=278) believing incorrectly that IMD is a viral infection. 36.6% (n=1,114) had low overall knowledge of IMD. Adolescents ($p<0.050$), non-Australian born ($p<0.001$), low educational attainment ($p=0.019$), low household income ($p=0.011$), low/medium socio-economic status ($p<0.050$) or living in a metropolitan area ($p=0.006$) were more likely to have lower overall knowledge of IMD. Participants who were not parents ($p<0.001$), male gender ($p<0.001$), single ($p<0.001$), highly educated ($p=0.022$) or had high household income ($p=0.015$), had lower concern about IMD.

Conclusion: Large community knowledge gaps for IMD were observed, particularly amongst adolescents and adults with low educational attainment and low socio-economic status. Improving community knowledge of IMD could help ensure optimal uptake of a new meningococcal vaccine. Our study results can help guide development of community tailored immunisation education programs.

Key words: Meningococcal disease, knowledge, awareness, survey

Abbreviations:

IMD	Invasive meningococcal disease
MenB	Meningococcal B
PBAC	Pharmaceutical Benefits Advisory Committee
SEIFA	Socio Economic Index for Areas

INTRODUCTION (word count 3021)

Invasive meningococcal disease (IMD) is characterised by its rapid onset, high case fatality, high rate of incapacitating long-term sequelae, and is a leading infectious cause of death in childhood in industrialised countries.[1] The highest disease incidence occurs in children < 5 years and adolescents 15 – 24 years of age.[2] Clinical disease such as meningitis and septicaemia are caused by six of thirteen *Neisseria meningitidis* subgroups (A, B, C, W135, X and Y). Meningococcal vaccines are currently available in Australia to protect against meningococcal serogroups A, C, W135 and Y.[3] However, approximately 85% of serogroup-confirmed meningococcal cases are now caused by serogroup B, as the number of cases of other serogroups, particularly serogroup C, has declined since the implementation of universal meningococcal C childhood vaccination.[4, 5] A new meningococcal B (MenB) vaccine, Bexsero®, has recently been approved in the EU and Australia for use in individuals from two months of age. In its meeting in November 2013, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia did not recommend the inclusion of the multicomponent meningococcal B vaccine on the National Immunisation Program Schedule mainly because of its unfavourable cost-effective estimate and uncertain assumptions about vaccine effectiveness and large vaccination coverage required.[6] A resubmission is planned to address issues raised by the PBAC.[7]

Awareness and attitudinal research can not only give us in-depth insights into the general public's knowledge about IMD but can also provide useful information to regulatory authorities when considering funding and introduction of a new vaccination program. Such research enables us to understand motivations,

barriers, and other influential factors affecting vaccine implementation and also allow us to recognise the needs of different population groups.[8] Finding out public perception of the seriousness of the disease to be prevented by a new vaccine and addressing inaccuracies through targeted education and promotion, are imperative to achieving high coverage of a new vaccine[9], with consequential impact on its cost-effectiveness analysis. Surveys to evaluate the views of stakeholders and target groups are valuable for identifying challenges and opportunities prior to implementing a vaccination program.[10] Previous studies have indicated that public recognition of disease severity could play an important role in parental acceptance of a relevant vaccine.[11] Conversely, lack of disease specific knowledge could lead to poor compliance with new vaccines.[12, 13] The assessment of community knowledge and awareness of IMD is required to understand the general public's view of the disease in order to help decision makers and immunisation educators to develop community tailored educational programs targeted to specific groups to maximise vaccine coverage. High uptake of a vaccine with potential herd immunity benefits can affect cost-effectiveness results [14], and hence would be an important consideration in vaccine funding decision-making.

There is currently limited information regarding community, parental and adolescent knowledge and awareness of IMD. An online survey was conducted in seven countries including Australia, to investigate health care providers' and parents' knowledge and attitudes toward vaccine-preventable disease and introduction of new vaccines in infants.[15] The new MenB vaccine was used as an example to detect factors impacting vaccine decisions. It was concluded that

improving awareness of the vaccine-preventable disease would be essential for a high vaccine uptake. As an online survey, study results were subject to selection bias with limited generalisability of the study results.

Two other studies in the Netherlands and Auckland have also assessed parental awareness of IMD and suggested that the vast majority of parents were aware of the severity of IMD and that perceived vulnerability was associated with a more positive attitude towards vaccination, however these studies are both limited by selection bias and may not be generalisable to the population.[16-18]

This current, large population study aimed to assess knowledge and concern about IMD and perception of disease severity, incidence and susceptibility in the South Australian community and determine factors associated with lower or higher knowledge and concern prior to the introduction of the new MenB vaccine.

METHODS

This cross-sectional study was conducted by face to face interviews in South Australia. 5,200 households were randomly selected according to the collectors' districts used by the Australian Bureau of Statistics in the 2006 Census and stratified by metropolitan or rural location.[19] The person in the household, who most recently celebrated their birthday and was 15 years or older, was interviewed (one interview per household).

Questions were asked to assess general understanding and perception of severity, incidence and susceptibility to IMD, and concerns about IMD (Figure 1). Detailed demographic details were collected including age, gender, country of birth, marital status, family composition, educational attainment, work status and household income.

Statistical analyses were performed using Stata, version 11 (StataCorp) with the survey data weighted in accordance with 2011 Census figures to provide a demographic description of the South Australian population by age and gender. The weighting process ensured our findings were representative of the South Australian population as a whole. Descriptive results were reported for demographic data. An open ended question was used to gauge the general understanding of IMD in the community.

The outcome measures included an overall score of knowledge of IMD and concern about the disease. Answers to three questions on knowledge of severity, incidence and susceptibility to IMD were dichotomised as "correct" or "incorrect".

When the participant chose a correct answer to one question, one score was given to the participant. The overall score was calculated as the total scores of these three questions. Participants who answered at least two of these three questions correctly were considered to have a higher overall score (2 – 3). An overall score less than two was categorised as a lower overall score (0 – 1). The participants were asked to assess their concern about IMD on a scale of 0 to 10 with an opt-out option “refused” or “don’t know”. A level of 6 – 10 was classified as “higher concern” and a level of 0 – 5 was classified as “lower concern”.

The predictor variables were comprised of country of birth, marital status, educational attainment, work status, household income, gender, age, geographical area, socio-economic status and parental status of the participants (whether the participants were parents or not in the household). The levels of socio-economic status were determined by the Socio Economic Index for Areas (SEIFA) Index of Relative Socioeconomic Disadvantage.[20]

Univariate and multiple logistic regression analyses were performed to test association between predictor variables and outcome measures. Any above-mentioned covariates with a p-value ≤ 0.20 on a univariate analysis of association with an outcome measure, were included into a multivariate logistic model. All results presented in the univariate and multivariate analyses were weighted. A two-sided p-value of less than 0.05 was deemed to be statistically significant.

The study was approved by the Women's and Children's Health Network Human Research Ethics Committee and the University of Adelaide Human Research Ethics Committee.

RESULTS

Study population

Among 5,200 randomly selected households, 137 were not permanent tenants and were excluded. Of the remaining 5063 households, 3,055 participants were interviewed with a response rate of 60.3%. 2008 households did not complete interviews due to various reasons (refusal (n=1178), contact not being established after six attempts (n=460), mental incapacity (n=94), non-English speaker (n=88), other (n=188)). Interviews were conducted between 4th September and 12th December 2012. Over half the participants were Australian born (74.2%, n=2,267) and 54.6% were employed (n=1,668). Approximately 70% of households (n=2,131) did not contain children and one third of participants (31.8%, n=972) were parents in the households. 15.9% of participants were adolescents aged 15 – 24 years (15.9%, n=487) (Table 1).

General understanding of IMD

Almost a quarter of participants (23.5%, n=717) had no knowledge of IMD and 15.9% (n=486) understood that IMD was a bacterial infection with almost 10% of participants (n=278) believing incorrectly that IMD was a viral infection. There was a large variety of answers to the question “What do you understand by the term ‘meningococcal disease’?” with the majority of people able to identify some characteristics of IMD. Although IMD is rare, there was evidence of a close association with a case for two participants, one who described that their grandson had died of IMD with another participant indicating they knew a girl who underwent amputation of her arms and legs following IMD. Just over a quarter of participants

(30.4%, n=930) described IMD as “deadly”, “serious” or “severe” infection (Table 2).

Overall knowledge of IMD

In total, 63.4% of participants (n=1,933) answered at least two of three questions on severity, incidence and susceptibility to IMD correctly and were classified as having higher knowledge with 27.1% (n=827) answering only one question correctly and 9.4% (n=288) responding to all questions incorrectly.

The majority (87.2%, n=2,661) understood correctly that IMD was a severe or very severe disease. Birth country not Australia ($p<0.001$), single status ($p=0.008$), having not completed school ($p=0.006$), low household income ($p<0.050$), male gender ($p<0.001$), adolescents ($p<0.050$) or metropolitan residential area ($p=0.038$), were associated with a lower odds of responding correctly to the question on IMD severity. Most participants (69.6%, n=2,126) were incorrect in their knowledge of the incidence of IMD: 35.2% (n=1,074) answering that IMD was uncommon (incidence rate <1/100), but not rare (incidence rate <1/1000), 19.3% (n=589) believing that IMD was common (incidence rate >1/100), and 13.4% (n=409) not able to answer the question and 1.8% (n=53) considering IMD as “very common” (incidence rate >1/10). Participants who were born outside Australia ($p=0.010$), did not complete tertiary education ($p<0.005$), had low or medium household income ($p<0.050$), were females ($p<0.001$), were adolescents ($p=0.020$), or had low socio-economic status ($p=0.003$) were less likely to answer the question on IMD incidence correctly. More than half (55.3%, n=1,689) gave a correct answer to the question on IMD susceptibility and agreed children and/or

adolescents were the main groups affected, with one third (30.4%, n=929) describing incorrectly that IMD affected any age equally and 12.0% (n=367) being uncertain of the answer. Male gender (p=0.004), metropolitan residential area (p=0.003), and low or medium socio-economic status (p<0.050) were associated with answering the question on age group susceptibility incorrectly.

After adjusting for socio-demographic covariates, adolescents (p<0.050), being born outside Australia (p<0.001), low educational level (p=0.019), low household income (p=0.011), metropolitan residential area (p=0.006) and low/medium socio-economic status (p<0.050) were associated with a lower overall score of IMD knowledge (Table 3). No difference in levels of overall IMD knowledge was found between parents and non-parents (OR: 1.00 (95% CI: 0.75 – 1.33), p=0.996).

Adolescents had lower knowledge of IMD including severity (OR: 0.34 (95% CI: 0.18 – 0.64), p=0.001), incidence (OR: 0.56 (95% CI: 0.33 – 0.94), p=0.028) and susceptibility to IMD (OR: 0.86 (95% CI: 0.56 – 1.33), p=0.493) in comparison with adults aged ≥ 25 years after adjusting other covariates. In general, adolescents were less likely to gain a higher score of overall IMD knowledge (OR: 0.59 (95% CI: 0.38 – 0.92), p=0.020).

General concern about IMD

1,922 participants (62.9%) had lower concern (a score of 0 – 5) about IMD including 19.1% (n=585) who scored concern as zero. 965 participants (31.6%) expressed higher concern (a score of 6 – 10) about the disease consisting of 9.8% (n=301) being extremely concerned (a score of 10), with 105 (3.4%) refusing and

63 (2.1%) stating “don’t know”. Participants who were not parents (p<0.001), male gender (p<0.001), single (p<0.001), highly educated (p=0.022) or had high household income (p=0.015), were more likely to have lower concern about the disease (Table 4). In addition, the level of concern about IMD was not significantly associated with overall knowledge scores (p=0.171).

DISCUSSION

Our study results revealed sub-optimal understanding and large knowledge gaps of IMD, particularly amongst adolescents. Although around 60% of participants responded correctly to at least two of three questions on severity, incidence and susceptibility to IMD, a considerable number of participants were not aware of IMD or had misconceptions about the disease. Despite the seriousness of meningococcal disease, more than half of participants had lower concern about IMD. Our study identified a number of socio-demographic factors that were related to lower knowledge of IMD and lower concern about the disease which have previously been associated with low knowledge of vaccine preventable diseases.[21, 22]

Participants with a low level of educational attainment, household income or socio-economic status were more likely to have lower overall knowledge of IMD compared with those who had high educational attainment, household income or socio-economic status. Moreover, adolescents had lower knowledge of IMD in comparison with non-adolescents. As adolescents are a target group for MenB vaccination, increasing awareness and knowledge of IMD is a priority. In addition, it is important that the information is relevant to what adolescents want to and need to know and in a format that is applicable to help them make an informed decision about immunisations such as MenB.

In our study, parental status of participants was significantly associated with higher concern about IMD. A study in the Netherlands indicated parents overestimated the risk of being infected with the meningococcus and dying from IMD. This study

showed that highly educated parents were less worried and had lower perceived risk of IMD infection which is consistent with our findings.[17] Female participants were almost twice as likely to have higher concern about IMD than males. A similar gender association was found in web-based and community surveys about influenza showing female parents perceived a higher threat of influenza than males.[21, 23]

Although a high level of educational attainment or household income was significantly associated with lower concern and higher scores of overall knowledge of IMD, the lower concern and a higher level of knowledge of IMD were not related, indicating that increasing accurate disease specific knowledge may not influence concern. Previous survey studies support the finding that greater knowledge of disease is not associated with levels of anxiety or concern.[24, 25]

Previous research has indicated health education and improvement in public awareness of vaccine-preventable disease (e.g. IMD) could increase uptake of a new vaccine.[15, 22] A survey of influenza vaccines showed that lack of disease related knowledge and a lower perceived risk from infections could lead to vaccine declination.[26] A questionnaire survey in the UK and online survey study in the US revealed knowledge of the disease, particularly severity and susceptibility, affected parental acceptance of a new vaccine.[23, 27] Our study results provide community-specific information on general awareness, knowledge of severity, incidence and susceptibility, and overall concern about IMD, which can enable policy makers and immunisation educators to develop community-tailored and appropriate educational programs once a new MenB vaccine is available. For

example, participants born outside Australia were associated with a low level of IMD knowledge in our study. Information about IMD should be provided in a variety of languages to assist migrants who may originate from countries with lower incidence of IMD. Our findings can assist in increasing awareness of the severity of IMD and correcting any misconceptions effectively by targeting simple but specific information to address these inaccuracies. For example, around 10% of participants confused IMD with a viral infection or flu, when in fact, it is a bacterial infection associated with poorer prognosis and higher case fatality rates than influenza, a most common viral infection. Furthermore, understanding of community knowledge of the disease could be helpful for health care providers to target specific groups with less knowledge to efficiently improve uptake of a new vaccine and empower individuals to make more informed decisions around vaccination. Vaccination coverage rates affect economic evaluations of vaccines[28] and high uptake of a vaccine with potential indirect population protection could add extra benefits to a vaccination program.[14] Engaging the community to improve public awareness of IMD and prevention by vaccination can identify the appropriate information and optimal delivery of that information. Awareness and attitudinal research is required, particularly involving adolescents, the highest at risk group with the lowest knowledge and concern and the group most likely to be targeted for a future MenB immunisation program.

Our study had several important strengths. Firstly, a large number of participants were randomly selected from the South Australian population and the survey data were weighted to report on the population level improving generalisability of our findings. In addition, we were able to assess adolescent's knowledge of

meningococcal disease, an important target group for MenB immunisation. Furthermore, in-depth socio-demographic data were collected which were essential to investigate which socio-demographic groups had low knowledge and awareness of IMD. Lastly, as the survey was conducted through face to face interviews, it may be easier for interviewers and participants to either clarify answers or questions so results are more likely to be an accurate representation of knowledge than other forms of interviews. However, there is the potential that social desirability responses in a face to face interview may bias the results. This was a cross sectional study and therefore has some additional limitations as the study was conducted at one point in time. The survey was conducted in 2012 prior to licensing of the MenB vaccine. News and new promotional programs may raise public awareness of the disease once the vaccine is available for private purchase. Forty percent of households approached did not participate in the survey. Since no socio-demographic information was obtained from the non-responders, there may be a nonresponse bias that was unable to be assessed in our study. Non-English speakers were not included in the study. Nonetheless, the proportion of non-English speakers excluded from the study was small, so is likely to have limited impact on the study results. The interviews were conducted in South Australia, and although results were generalizable to the population of South Australia, they may not be generalizable to the Australian population as a whole.

As serogroup B IMD predominates in Australia, accounting for around 85% of 241 laboratory-confirmed IMD cases in 2011,[5] high uptake of the new MenB vaccine would be required to reduce the incidence of IMD and relieve the economic burden of the disease. The delivery of community tailored educational programs and

informational materials can help to achieve high coverage by targeting those with the least knowledge and lowest concern about IMD once a MenB vaccine is available. If Bexsero® is not funded on the National Immunisation Program but available only on the private market, community perceptions and understanding will be key to optimising vaccine uptake and protection for the community.

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COMPETING INTERESTS

Associate Professor Helen Marshall has been a member of vaccine advisory boards for GlaxoSmithKline Biologicals and Wyeth, and has received travel support from CSL, Pfizer, Novartis, and GlaxoSmithKline Biologicals to present scientific data at international meetings. Her institution has received funding for investigator-led research from GlaxoSmithKline, Sanofi-Pasteur, and Novartis Vaccines. Ms Michelle Clarke has received a travel support grant from GlaxoSmithKline to present independent research at a national conference. There are no other conflicts of interest to declare.

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and conducted independently of the sponsors with the analyses and writing of the publication completed by the listed authors.

CONTRIBUTOR STATEMENT

BW performed the data analyses and prepared the first draft of the manuscript under direct supervision of HM and HH. HH contributed to and reviewed and edited the manuscript. HM assisted in study design and contributed to and reviewed the manuscript. MC assisted in study design and reviewed and edited the manuscript. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all authors.

SUBMISSION DECLARATION AND VERIFICATION

All authors acknowledge that the article has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

TRIAL REGISTRATION NUMBER

This study has not been registered in a clinical trial registry because it was not a clinical trial and therefore registration was not required.

REFERENCE

1. Hart CA, Thomson AP. Meningococcal disease and its management in children. *BMJ (Clinical research ed).* 2006;333(7570):685-90.

2. Chiu C, Dey A, Wang H, Menzies R, Deeks S, Mahajan D, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2005 to 2007. *Commun Dis Intell.* 2010;34(Supplement):S50-6.

3. *The Australian Immunisation Handbook* 10th edition 2013. Department of Health and Aging, Australia.

4. Annual report of the Australian Meningococcal Surveillance Programme, 2001. *Commun Dis Intell Q Rep.* 2002;26(3):407-18.

5. Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2011. *Commun Dis Intell Q Rep.* 2012;36(3):E251-62.

6. *November 2013 PBAC Outcomes - 1st Time Decisions Not to Recommend,* Pharmaceutical Benefits Advisory Committee (PBAC), The Department of Health, Commenwealth of Australia, viewed 31 Jan 2014, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2013-11>

7. "Patients want "compassion" on meningococcal vaccine", *PharmaDispatch*, viewed 31 Jan 2014, <http://www.pharmadispatch.com/patients-want-compassion-on-meningococcal-vaccine/>

8. Snape MD, Medini D, Halperin SA, DeTora L, Drori J, Moxon ER. The challenge of post-implementation surveillance for novel meningococcal vaccines. Vaccine. 2012 30;30 Suppl 2:B67-72.

9. Noakes K, Yarwood J, Salisbury D. Parental response to the introduction of a vaccine against human papilloma virus. Hum Vaccin. 2006;2(6):243-8.

10. Ortiz JR, Neuzil KM, Ahonkhai VI, Gellin BG, Salisbury DM, Read JS, et al. Translating vaccine policy into action: a report from the Bill & Melinda Gates Foundation Consultation on the prevention of maternal and early infant influenza in resource-limited settings. Vaccine. 2012;30(50):7134-40

11. Yarwood J, Noakes K, Kennedy D, Campbell H, Salisbury D. Tracking mothers attitudes to childhood immunisation 1991-2001. *Vaccine.* 2005;23(48-49):5670-87.

12. Dorell C, Yankey D, Strasser S. Parent-reported reasons for nonreceipt of recommended adolescent vaccinations, national immunization survey: teen, 2009. *Clin Pediatr (Phila)*. 2011;50(12):1116-24.

13. Hak E, Schonbeck Y, De Melker H, Van Essen GA, Sanders EA. Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program. *Vaccine.* 2005;23(24):3103-7.

14. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine*. 2013;31(23):2638-46.

15. Bakhache P, Rodrigo C, Davie S, Ahuja A, Sudovar B, Crudup T, et al. Health care providers' and parents' attitudes toward administration of new infant vaccines--a multinational survey. *Eur J Pediatr*. 2013;172(4):485-92.

16. Petousis-Harris H, Turner N, Soe B. Parent views on school based immunisation: A survey of parents of year 1 and 6 in three diverse Auckland schools. *N Z Fam Physician.* 2004;31(4):222-8.

17. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Attitudes and risk perception of parents of different ethnic backgrounds regarding meningococcal C vaccination. *Vaccine.* 2005;23(25):3329-35.

18. Timmermans DR, Henneman L, Hirasing RA, van der Wal G. Parents' perceived vulnerability and perceived control in preventing Meningococcal C infection: a large-scale interview study about vaccination. *BMC Public Health*. 2008;8:45.

19. *Health Omnibus Survey Methodology Brief Report* 2012. Population Research and Outcomes Studies Unit, The University of Adelaide.

20. Pink B. Information paper: an introduction to socio-economic indexes for areas (SEIFA), 2006. Canberra: Australian Bureau of Statistics (ABS); 2008

21. Marshall H, Tooher R, Collins J, Mensah F, Braunack-Mayer A, Street J, et al. Awareness, anxiety, compliance: community perceptions and response to the threat and reality of an influenza pandemic. *Am J Infect Control.* 2012;40(3):270-2.

22. Marshall H, Ryan P, Roberton D, Baghurst P. A cross-sectional survey to assess community attitudes to introduction of Human papillomavirus vaccine. *Aust N Z J Public Health*. 2007;31(3):235-42.

23. Flood EM, Rousculp MD, Ryan KJ, Beusterien KM, Divino VM, Toback SL, et al. Parents' decision-making regarding vaccinating their children against influenza: A web-based survey. *Prev Med (Baltim).* 2010;32(8):1448-67.

24. Goodman E, Cohall AT. Acquired immunodeficiency syndrome and adolescents: knowledge, attitudes, beliefs, and behaviors in a New York City adolescent minority population. *Pediatrics*. 1989;84(1):36-42.

25. Robb KA, Miles A, Campbell J, Evans P, Wardle J. Can cancer risk information raise awareness without increasing anxiety? A randomized trial. *Prev Med.* 2006;43(3):187-90.

26. Eppes C, Wu A, You W, Cameron KA, Garcia P, Grobman W. Barriers to influenza vaccination among pregnant women. *Vaccine.* 2013;31(27):2874-8.

27. Bedford H, Lansley M. More vaccines for children? Parents' views. *Vaccine.* 2007;25(45):7818-23.

28. Pitman RJ, Nagy LD, Sculpher MJ. Cost-effectiveness of childhood influenza vaccination in England and Wales: Results from a dynamic transmission model. *Vaccine*. 2013;31(6):927-42.

Table 1: Socio-demographic characteristics

Variables	Number	Weighted Number*	Weighted Percent*	95% Confidence Interval
Age				
15 – 24 (adolescents)	306	487	15.9	14.2 – 17.7
25 – 54 (young and middle aged adults)	1,389	1,501	49.1	47.1 – 51.2
55+ (older adults)	1,360	1,066	34.9	33.1 – 36.7
Gender				
Male	1,279	1,494	48.9	46.9 – 50.9
Female	1,776	1,561	51.1	49.1 – 53.1
Country of birth				
Non-Australia	792	787	25.8	24.0 – 27.5
Australia	2,262	2,267	74.2	72.5 – 76.0
Marital Status				
Married/De Facto	1,719	1,905	62.4	60.5 – 64.4
Single	1,333	1,147	37.6	35.6 – 39.5
Educational attainment				
Lower than Year 12 education	1,113	1,063	34.8	32.9 – 36.7
Higher than or equal to Year 12 education/trade/certificate/diploma	1,281	1,307	42.8	40.9 – 44.8
Degree or higher	655	682	22.3	20.7 – 24.0
Work status				
Employed	1,561	1,668	54.6	52.6 – 56.6
Unemployed	288	300	9.8	8.6 – 11.0
Retired	850	614	20.1	18.7 – 21.5
Student	192	330	10.8	9.3 – 12.3
Other	163	144	4.7	3.9 – 5.5
Household income				
Low (≤ AUD $40,000)	820	583	27.7	25.8 – 29.6
Medium (AUD $40,001 – $80,000)	603	582	27.6	25.6 – 29.7
High (≥ AUD $80,001)	821	941	44.7	42.3 – 47.0
Area				
Metropolitan	2,241	2,235	73.2	71.4 – 75.0
Rural	814	820	26.8	25.0 – 28.6
Socio-economic status				
Low (1st – 33rd percentile)	1,144	1,160	38.0	36.0 – 39.9
Medium (34th – 66th percentile)	938	907	29.7	27.9 – 31.5
High (67th – 100th percentile)	973	988	32.3	30.5 – 34.2
Total number of children in household				
0	2,131	2,131	69.8	68.1 – 71.4
1	346	346	11.3	10.2 – 12.5
2	397	397	13.0	11.8 – 14.2
3+	180	180	5.9	5.1 – 6.7
Total number of people in household				
1	759	759	24.8	23.33 – 26.4
2	1,138	1,138	37.3	35.5 – 39.0
3	432	432	14.1	12.9 – 15.4
4	477	477	15.6	14.3 – 16.9
5+	249	249	8.2	7.2 – 9.1
Participant's parental status				
No	2,220	2,080	68.2	66.2 – 70.1
Yes	834	972	31.8	29.9 – 33.8

* All results were weighted by the inverse of the individual's probability of selection and the response rate in metropolitan and country regions, and then re-weighted to benchmarks derived from the 2011 Estimated Residential Population based on 2011 Population Census.

Table 2 Descriptive results of general understanding of invasive meningococcal disease

General understanding of IMD	Number	Weighted Number*	Weighted Percent*	95% Confidence Interval
Don't know	654	717	23.5	21.7 – 25.3
Bacterial infection that can be deadly	490	486	15.9	14.5 – 17.4
Meningitis – inflammation in the tissue	447	419	13.7	12.4 – 15.1
Virus/viral infection	286	278	9.1	8.0 – 10.3
Rash/spots/fever	270	260	8.5	7.4 – 9.6
Life threatening/deadly	223	212	6.9	6.0 – 7.9
Others	157	165	5.4	4.5 – 6.3
Serious/dangerous/severe	118	119	3.9	3.2 – 4.7
Severe infection resulting in amputation	110	113	3.7	2.9 – 4.4
Flesh eating infection	105	103	3.4	2.7 – 4.1
Brain disease/affects brain	54	51	1.7	1.2 – 2.2
Waterborne infection	31	27	0.9	0.5 – 1.2
Affects young people	30	29	0.9	0.6 – 1.3
Blood disease/affects blood	27	25	0.8	0.5 – 1.2
Flu like illness	20	20	0.7	0.3 – 1.0
An infection	15	13	0.4	0.2 – 0.7
Contagious	15	14	0.5	0.2 – 0.7

* All results were weighted by the inverse of the individual's probability of selection and the response rate in metropolitan and country regions, and then re-weighted to benchmarks derived from the 2011 Estimated Residential Population based on 2011 Population Census.

Table 3 Predictors of participants with a higher overall knowledge score of invasive meningococcal disease *

Variables	Participants with a higher overall score (2-3)[#]		Participants with a lower overall score (0-1)[#]		Univariate Associations			Multivariate Logistic Regression Analysis		
					Odds Ratio	95% Confidence Interval	p-value	Adjusted Odds Ratio	95% Confidence Interval	p-value
Age	**n**	**%**	**n**	**%**			**<0.001**			**0.067**
15 – 24 (adolescents)	219	45.1	266	54.9	1.00	-		-	-	-
25 – 54 (young and middle aged adults)	1,019	68.0	480	32.0	2.59	1.97 – 3.40	<0.001	1.68	1.07 – 2.64	0.023
55+ (older adults)	695	65.4	368	34.6	2.30	1.75 – 3.02	<0.001	1.69	1.03 – 2.77	0.038
Gender	**n**	**%**	**n**	**%**						
Male	937	62.9	553	37.1	1.00	-		-	-	-
Female	996	64.0	561	36.0	1.05	0.88 – 1.24	0.586	-	-	-
Country of birth	**n**	**%**	**n**	**%**						
Non-Australia	420	53.5	366	46.5	1.00	-		-	-	
Australia	1,152	66.9	749	33.1	1.76	1.46 – 2.12	<0.001	1.55	1.23 – 1.98	<0.001
Marital Status	**n**	**%**	**n**	**%**						
Married/De Facto	1,289	67.8	612	32.2	1.00	-		-	-	
Single	643	56.2	501	43.8	0.61	0.51 – 0.72	<0.001	0.99	0.79 – 1.25	0.939
Educational attainment	**n**	**%**	**n**	**%**			**<0.001**			**0.055**
Lower than Year 12 education	601	56.7	459	43.3	1.00	-		-	-	
Higher than or equal to Year 12 education/trade/ certificate/diploma	842	64.6	461	35.4	1.39	1.15 – 1.69	0.001	1.22	0.96 – 1.56	0.099
Degree or higher	489	71.8	192	28.2	1.95	1.53 – 2.48	<0.001	1.47	1.06 – 2.02	0.019
Work status	**n**	**%**	**n**	**%**			**<0.001**			**0.660**
Employed	1,232	68.0	532	32.0	1.00	-		-	-	
Unemployed	179	59.8	120	40.2	0.70	0.52 – 0.94	0.016	0.93	0.64 – 1.35	0.709
Retired	388	63.3	225	36.7	0.81	0.67 – 0.98	0.033	1.16	0.81 – 1.64	0.418
Student	150	45.6	179	54.4	0.39	0.28 – 0.55	<0.001	0.81	0.45 – 1.45	0.474
Other	84	59.2	58	40.8	0.68	0.47 – 0.99	0.044	0.85	0.53 – 1.35	0.482
Household income	**n**	**%**	**n**	**%**			**<0.001**			**0.039**
Low (≤ AUD $40,000)	365	62.9	215	37.1	1.00	-		-	-	
Medium (AUD $40,001 – $80,000)	398	68.4	184	31.6	1.28	0.99 – 1.64	0.056	1.25	0.93 – 1.67	0.135
High (≥ AUD $80,001)	699	74.5	239	25.5	1.72	1.36 – 2.18	<0.001	1.53	1.10 – 2.14	0.011
Area	**n**	**%**	**n**	**%**						
Metropolitan	1,394	62.6	835	37.4	1.00	-		-	-	
Rural	539	65.8	280	34.2	1.15	0.95 – 1.40	0.155	1.44	1.11 – 1.87	0.006
Socio-economic status	**n**	**%**	**n**	**%**			**0.001**			**0.006**
Low (1st – 33rd percentile)	692	59.8	465	40.2	1.00	-		-	-	
Medium (34th – 66th percentile)	564	62.4	341	37.6	1.11	0.91 – 1.36	0.303	1.06	0.82 – 1.36	0.672
High (67th – 100th percentile)	676	68.7	309	31.3	1.47	1.20 – 1.81	<0.001	1.54	1.16 – 2.05	0.003
Participant's parental status	**n**	**%**	**n**	**%**						
No	1,293	62.3	782	37.7	1.00	-		-	-	-
Yes	637	65.7	333	34.3	1.16	0.96 – 1.40	0.130	1.00	0.75 – 1.33	0.996

* All results were weighted by the inverse of the individual's probability of selection and the response rate in metropolitan and country regions, and then re-weighted to benchmarks derived from the 2011 Estimated Residential Population based on 2011 Population Census.

Three questions on knowledge of severity, incidence and susceptibility to IMD were used to assess the overall knowledge of meningococcal disease for each participant. Participants who answered at least two of these three questions correctly, had a higher overall score (2 – 3). An overall score less than two was categorised as a lower overall score (0 – 1).

Table 4 Predictors of participants with higher concern of invasive meningococcal disease*

Variables	Participants with higher concern# (6 – 10)		Participants with lower concern# (0 – 5)		Univariate Associations			Multivariate Logistic Regression Analysis		
					Odds Ratio	95% Confidence Interval	p-value	Adjusted Odds Ratio	95% Confidence Interval	p-value
Age	**n**	**%**	**n**	**%**			**0.001**			**0.257**
15 – 24 (adolescents)	104	23.5	340	76.5	1.00	-		-	-	
25 – 54 (young and middle aged adults)	506	35.3	927	64.7	1.78	1.29 – 2.45	<0.001	1.25	0.75 – 2.08	0.400
55+ (older adults)	355	35.1	656	64.9	1.76	1.28 – 2.43	0.001	1.52	0.88 – 2.64	0.135
Gender	**n**	**%**	**n**	**%**						
Male	374	26.7	1,204	73.3	1.00	-		-	-	
Female	591	39.7	898	60.3	1.80	1.51 – 2.16	<0.001	1.75	1.41 – 2.17	<0.001
Country of birth	**n**	**%**	**n**	**%**						
Non-Australia	213	31.0	475	69.0	1.00	-		-	-	
Australia	752	34.2	1,447	65.8	1.16	0.94 – 1.42	0.159	1.04	0.82 – 1.33	0.740
Marital Status	**n**	**%**	**n**	**%**						
Married/De Facto	696	38.1	1,130	61.9	1.00	-		-	-	
Single	268	25.3	791	74.7	0.55	0.46 – 0.66	<0.001	0.62	0.49 – 0.79	<0.001
Educational attainment	**n**	**%**	**n**	**%**			**<0.001**			**0.065**
Lower than Year 12 education	378	37.9	619	62.1	1.00	-		-	-	
Higher than or equal to Year 12 education/trade/ certificate/diploma	414	33.1	838	66.9	0.81	0.67 – 0.98	0.031	0.90	0.70 – 1.15	0.410
Degree or higher	172	27.0	465	73.0	0.61	0.47 – 0.77	<0.001	0.69	0.50 – 0.95	0.022
Work status	**n**	**%**	**n**	**%**			**<0.001**			**0.965**
Employed	532	33.3	1,064	66.7	1.00	-		-	-	
Unemployed	122	43.5	159	56.5	1.54	1.15 – 2.05	0.003	0.98	0.67 – 1.42	0.901
Retired	199	34.8	373	65.2	1.07	0.87 – 1.30	0.525	0.94	0.67 – 1.31	0.712
Student	57	19.3	239	80.7	0.48	0.31 – 0.74	0.001	0.87	0.41 – 1.85	0.722
Other	54	38.5	87	61.5	1.25	0.86 – 1.83	0.247	1.11	0.68 – 1.81	0.666
Household income	**n**	**%**	**n**	**%**			**0.008**			**0.051**
Low (≤ AUD $40,000)	221	39.9	333	60.1	1.00	-		-	-	
Medium (AUD $40,001 – $80,000)	206	36.6	357	63.4	0.87	0.68 – 1.11	0.257	0.79	0.59 – 1.05	0.110
High (≥ AUD $80,001)	290	31.7	626	68.3	0.70	0.55 – 0.88	0.002	0.65	0.47 – 0.92	0.015
Area	**n**	**%**	**n**	**%**						
Metropolitan	651	31.0	1,451	69.0	1.00	-		-	-	
Rural	314	40.0	471	60.0	1.48	1.22 – 1.80	<0.001	1.23	0.95 – 1.59	0.122
Socio-economic status	**n**	**%**	**n**	**%**			**<0.001**			**0.325**
Low (1st – 33rd percentile)	416	38.4	665	61.6	1.00	-		-	-	
Medium (34th – 66th percentile)	275	31.9	589	68.1	0.75	0.61 – 0.92	0.007	0.85	0.66 – 1.09	0.204
High (67th – 100th percentile)	274	29.1	668	70.9	0.66	0.53 – 0.81	<0.001	0.82	0.62 – 1.10	0.191
Participant's parental status	**n**	**%**	**n**	**%**						
No	563	28.9	1,387	71.1	1.00	-		-	-	
Yes	402	43.0	532	57.0	1.86	1.54 – 2.24	<0.001	2.09	1.58 – 2.78	<0.001

* All results were weighted by the inverse of the individual's probability of selection and the response rate in metropolitan and country regions, and then re-weighted to benchmarks derived from the 2011 Estimated Residential Population based on 2011 Population Census.

The concern about invasive meningococcal disease was assessed on a scale of 0 to 10. A level of 6 – 10 was classified as "higher concern" and a level of 0 – 5 was classified as "lower concern".

Figure 1 Interview questions on understanding and concern about invasive meningococcal disease

General Understanding of invasive meningococcal disease
• What do you understand by the term 'meningococcal disease'? (open-ended question)
Understanding of severity of invasive meningococcal disease
• Which do you believe best describe your understanding of meningococcal disease in terms of severity? 6. Mild disease 7. Moderately Severe (may require hospitalisation) 8. Severe (requires hospitalisation) 9. Very Severe (may be life threatening or fatal) 10. Don't know/Unsure
Understanding of incidence of invasive meningococcal disease
• Which do you believe best describe your understanding of meningococcal disease in terms of incidence? 6. Rare (affects less than 1/1000 people) 7. Uncommon (affects less than 1/100 people) 8. Common (affects more than 1/100 people) 9. Very common (affects more than 1/10 people) 10. Don't know/Unsure
Understanding of susceptibility to invasive meningococcal disease
• Which do you believe best describe your understanding of meningococcal disease in terms of people affected? 8. Mostly children 9. Mostly adolescents 10. Mostly children or adolescent 11. Mostly elderly 12. Mostly people with other medical conditions 13. Any age equally 14. Don't know/Unsure
Overall concern about invasive meningococcal disease
• On a scale of 0 – 10 where 0 means you are not concerned at all and 10 means you are extremely concerned, how concerned are you about meningococcal disease? Enter number 0 – 10 ☐☐ or R for "Refused"