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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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