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AMEND study protocol: a case–control study to assess the long-term impact of invasive meningococcal disease in Australian adolescents and young adults

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ABSTRACT

Introduction Invasive meningococcal disease (IMD) primarily causes disease in young children and adolescents and can cause long-term disability. Many countries are considering implementation of meningococcal B and/or meningococcal ACWY vaccines to control meningococcal disease. Estimating the cost-effectiveness of meningococcal vaccine programme is hampered due to a lack of good quality costing and burden of disease data. This study aims to address this evidence gap by assessing the clinical, physical, neurocognitive, economic and societal impact of IMD on adolescents and young adults.

Methods and analysis A case–control study of 64 participants with confirmed IMD (15–24 years 11 months at time of disease) and 64 control participants (17–34 years 11 months) will be conducted in Australia from 2016 to 2020. All participants will undergo a neurocognitive assessment, full medical examination, pure tone audiometry assessment and complete quality of life and behavioural questionnaires. Meningococcal cases will be assessed 2–10 years posthospitalisation and a subset of cases will be interviewed to explore in depth their experiences of IMD and its impact on their life. Primary outcome measures include general intellectual functioning from the Wechsler Adult Intelligence Scale and overall quality of life from the Health Utilities Index. Secondary outcome measures include academic achievement, executive functioning, behaviour, hearing, psychological and physical functioning. Outcome measures will be compared between cases and controls using independent t-tests or ORs, or if any significant confounders are identified, adjusted analyses (analysis of covariance or adjusted ORs) will be conducted. Thematic analysis will be used to analyse transcribed interviews and a costing model will be used to project lifetime costs.

Ethics and dissemination The Adolescent MENingococcal Disease (AMEND) study has been approved by the Human Research Ethics Committee of the Women's and Children's Health Network (HREC/14/WCHN/024). The results will be disseminated via peer-reviewed publications, conference presentations, study participants, and meningococcal and meningitis foundations.

Trial registration number NCT03798574.

Strengths and limitations of this study

- Generation of new evidence to inform vaccination policy for protecting adolescents and young adults from invasive meningococcal disease (IMD).
- Comprehensive assessment of the long-term effects of meningococcal disease on adolescents and young adults including clinical, neurocognitive and quality of life.
- National recruitment of adolescents and young adults with IMD ensures generalisability of the data to Australia and similar countries, such as New Zealand, Canada, the UK and the USA.
- There is the potential for selection bias to occur since the sampling of cases and controls is occurring using different methods.
- While data obtained from self-reported questionnaires and interviews provide valuable information about participants' perceptions of their own functioning, we cannot be confident that participants have provided accurate data free from recall or other bias.

INTRODUCTION

Invasive meningococcal disease (IMD) is one of the most common infectious causes of death in childhood in developed countries.[1] *Neisseria meningitidis*, the cause of meningococcal disease, causes significant morbidity and mortality worldwide with approximately 500 000–1 200 000 cases and 50 000–135 000 deaths reported annually.[2 3] IMD often manifests as septicaemia without or with meningitis[4] and can cause permanent sequelae, which may lead to significant disability in approximately 7.2% (4.3%–11.2%) of survivors.[5]

Survivors of IMD often experience a range of cognitive, psychosocial and physical sequelae that are mild to severe in nature and impact on their health-related quality of life (QoL). These sequelae occur both in

the short-term and long-term post-IMD and have been reported in child and adult survivors.[6 7] A large case–control study conducted in England found that around 10% of children approximately 3 years post-serogroup B IMD (mean age 6 years old at time of assessment) had a major disabling deficit. In addition, more than one-third of IMD cases (36%) had one or more deficits in physical, cognitive and psychological functioning versus 15% of controls.[7] However, while these deficits were relatively common, their impact on the QoL of children was not examined.

While meningococcal disease affects all age groups, the incidence of IMD peaks in the 0–4 years, and 15–25 years age groups in some countries, including Australia.[8–10] To date, few studies have examined the long-term impact of IMD on adolescents and young adults (AYA) aged 15–25 years at the time of disease. This is an important transition period when AYA are learning to be responsible for their own medical care while experiencing many unmet healthcare needs and difficulties in accessing healthcare,[11] as well as completing secondary schooling and planning for future tertiary options and/or employment. It is also a crucial developmental period associated with significant maturational changes in brain structure, neurochemistry and function, as well as changes in cognition and emotion, with increased risk-taking behaviour and onset of mental illness frequently occurring during this period.[12 13] The results from a study of young adult males (18–24 years at the time of IMD) conducted over 30 years ago indicated that 3–15 years post-IMD, survivors reported significantly more symptoms of possible sequelae compared with the control group (61% vs 20%).[14] In addition, around 30% reported that the disease had affected their education or working capacity.[14] In another study adolescents (15–19 years at time of IMD) who were followed up 18–36 months post-disease also reported poorer educational attainment, achieving fewer passes at high school and were twice as likely to have failed an examination in the last 12 months when compared with matched controls.[6] Adolescent survivors also reported significantly poorer physical and mental health (ie, depression), as well as QoL when compared with controls. Disabling physical sequelae were identified in 57% of survivors and 5% required amputations.[6]

While IMD has a low incidence, it is associated with significant economic implications. A recent systematic review of studies that reported the financial costs associated with acute and long-term sequelae of IMD found that while IMD results in significant costs to healthcare systems, costing for long term and indirect costs are lacking.[15] In addition, as the costs of hospitalisation and follow-up care reported in these studies were estimated only from a third-party payer's perspective, it is likely that the societal burden of IMD was underestimated.[15] Further studies of indirect costs of IMD are imperative to estimate the total financial burden of IMD.

The health economic evaluation of meningococcal vaccine programmes has identified that further data on long-term sequelae would be beneficial.[16] For vaccines against uncommon diseases, like IMD, the results of health economic evaluations can vary significantly depending on the parameter values used (eg, treatment costs, QoL losses of IMD) or on the basis of expert opinions.[17 18] Cost-effectiveness analyses are challenging due to a paucity of data on disease burden, particularly a lack of data on long-term disability from IMD, making decisions on the introduction of meningococcal vaccination programme difficult.[19]

Although meningococcal vaccines are licensed in many countries, they are not necessarily publicly funded due to unknown or unfavourable cost-effectiveness analyses.[20] Only the UK has introduced a national funded MenB vaccine programme that is provided for infants. Due to increasing incidence of meningococcal W IMD cases in the UK, a funded MenACWY vaccine programme has been introduced.[21] In Australia, a MenACWY programme has been introduced for infants at 1 year of age and will be funded for adolescents 14–19 years of age from 2019.[22] However, none of these programmes provides full protection against all meningococci, so disease will continue to be a burden in these age groups. Health authorities in several countries, such as Spain, are considering the introduction of MenB and MenACWY vaccines in their national immunisation programme, but detailed and contemporary data on the clinical benefit and long-term costs are not available, particularly for AYA.[23]

The findings from this study will assist in more robust data to inform policy as to whether meningococcal vaccines should be included in routine immunisation programme. Additionally, cost of illness studies can produce estimates of the real economic consequence over time of a specific disease and assist in understanding the importance of a particular health problem, particularly for a rare disease, such as meningococcal infection.[24] Such studies can also be used to aid policy-makers to estimate cost savings and medical benefits in economic evaluations of healthcare interventions and to inform public health policies, such as funding priorities and immunisation programmes.[25–27]

In summary, survivors of IMD experience a range of mild to severe sequelae that impact on their QoL. The majority of studies to date have focused on the impact of IMD on childhood and very little is known about the impact of the disease on AYA. Given that this is a critical period, it is feasible that the impact of IMD disease during this time may be greater for AYA than younger children. In addition, there are no data on the long-term sequelae of IMD in survivors. Further research is warranted to understand the impact of sequelae of IMD on AYA, as well as the financial impact of the disease on individuals, their families and the healthcare system. Therefore, the overall aim of this study is to assess the physical, neurocognitive, economic and societal impact of IMD on AYA.

METHODS AND ANALYSIS

Study aims

The primary aim of this study is to determine the long-term impact of IMD on general intellectual functioning and QoL of AYA. Secondary aims include (1) assessing the impact of IMD on neurocognitive (academic achievement, executive functioning, memory), psychological and physical functioning; (2) estimating the lifetime costs associated with survival following IMD and (3) comparing the burden of serogroup B IMD to non-B serogroup IMD. An exploratory aim is to examine the relationship between meningococcal serogroup type and disease severity/sequelae.

Study design

This is a multicentre, case–control, mixed-methods complementarity study.

Study setting

Identification of IMD cases will occur at each of the participating Australian hospitals (paediatric and adult) in Adelaide (Women's and Children's Hospital, Flinders Medical Centre, Royal Adelaide Hospital, Lyell McEwin Hospital and The Queen Elizabeth Hospital), Sydney (Children's Hospital at Westmead, Westmead Hospital and Royal Prince Alfred Hospital), Melbourne (Monash Children's Hospital, Monash Medical Centre and The Alfred Hospital) and Perth (Princess Margaret Hospital for Children and Sir Charles Gairdner Hospital). Of note, in Australia, children aged from birth to 16 years (and up to 18 years for pre-existing conditions) are admitted to a children's hospital for medical care.

Study procedures

Prospective cases will be identified by hospital staff who will conduct a daily surveillance of their hospital systems for patients who are admitted with suspected meningococcal infection as reported in their medical records and also access hospital separation data to identify any admissions coded with International Classification of Diseases (ICD) 10-A39.0 to A39.9 (as a primary or additional code) or coded J15.8[28] (see figure 1). After a diagnosis of IMD has been confirmed (please see inclusion criteria) by site medical staff, the treating hospital physician will provide patients with a study information sheet requesting that they contact the study investigators if they would like to participate.

Retrospective cases who were hospitalised 2–10 years ago with confirmed IMD will be identified by site staff from discharge coding, hospital medical records and/or an electronic database of patients' diagnoses maintained by the Infectious Diseases Department of the hospital. After a diagnosis of IMD has been confirmed by site medical staff, participants/parents will be mailed a study invitation letter inviting them to contact the study investigators if they have any questions or would like further information about the study. If they do not respond, three attempts will be made by the site staff to contact them by mail/phone.

Controls will be prospectively recruited by 'snowballing sampling' technique whereby enrolled IMD cases will be asked to distribute a study information sheet to their friends/acquaintances who are approximately the same age.[29] Potential controls who would like further information or would like to participate will contact the site staff by phone/email. Control participants may also be identified through community advertising or from research databases at each participating site. These databases are managed by participating hospitals and contain contact details of the people who have previously consented to be contacted about participating in future studies. The majority have been community participants of previous studies conducted at the hospital. Controls will be group matched by age and gender. Enrolment of participants commenced from 2016 and is expected to be completed by December 2020.

Eligibility

Inclusion criteria

- Retrospective cases will be identified by using the following codes ICD 10-A39.0 to A39.9[28] or ICD 9–036 (as a primary or additional code) or coded J15.8.[28] All IMD cases (retrospective and prospective) must have a confirmed infection by PCR, culture or cerebrospinal fluid with *N. meningitidis* of any serogroup, which will be verified by the site nurse or doctor.
- IMD cases must be aged 15–24 years 11 months inclusive at the time of IMD and currently hospitalised for IMD or recently separated (prospective); or hospitalised for IMD within the previous 2–10 years at the time of study assessments (retrospective).
- Controls will be aged 17–34 years 11 months at the time of assessment. The older age matches the age range of IMD cases at the time of their assessment which is 2–10 years post-IMD.

Exclusion criteria

- Individuals who are not fluent with the English language since neurocognitive tests are only available in English.
- All participants with a known pre-existing intellectual disability and/or intracranial pathology (prior to hospitalisation for IMD cases).
- Control participants with a history of meningococcal disease.

Physical, neurocognitive and hearing outcomes

All participants will complete a neurocognitive and psychological assessment (see table 1) that will be conducted face to face by a psychologist and will take approximately 6 hours to complete. For all IMD cases (including those recruited prospectively), assessments will be conducted 2–10 years post-IMD admission. Psychologists conducting the assessments will be blinded (as far as possible) to case or control status. Participants will be advised not to

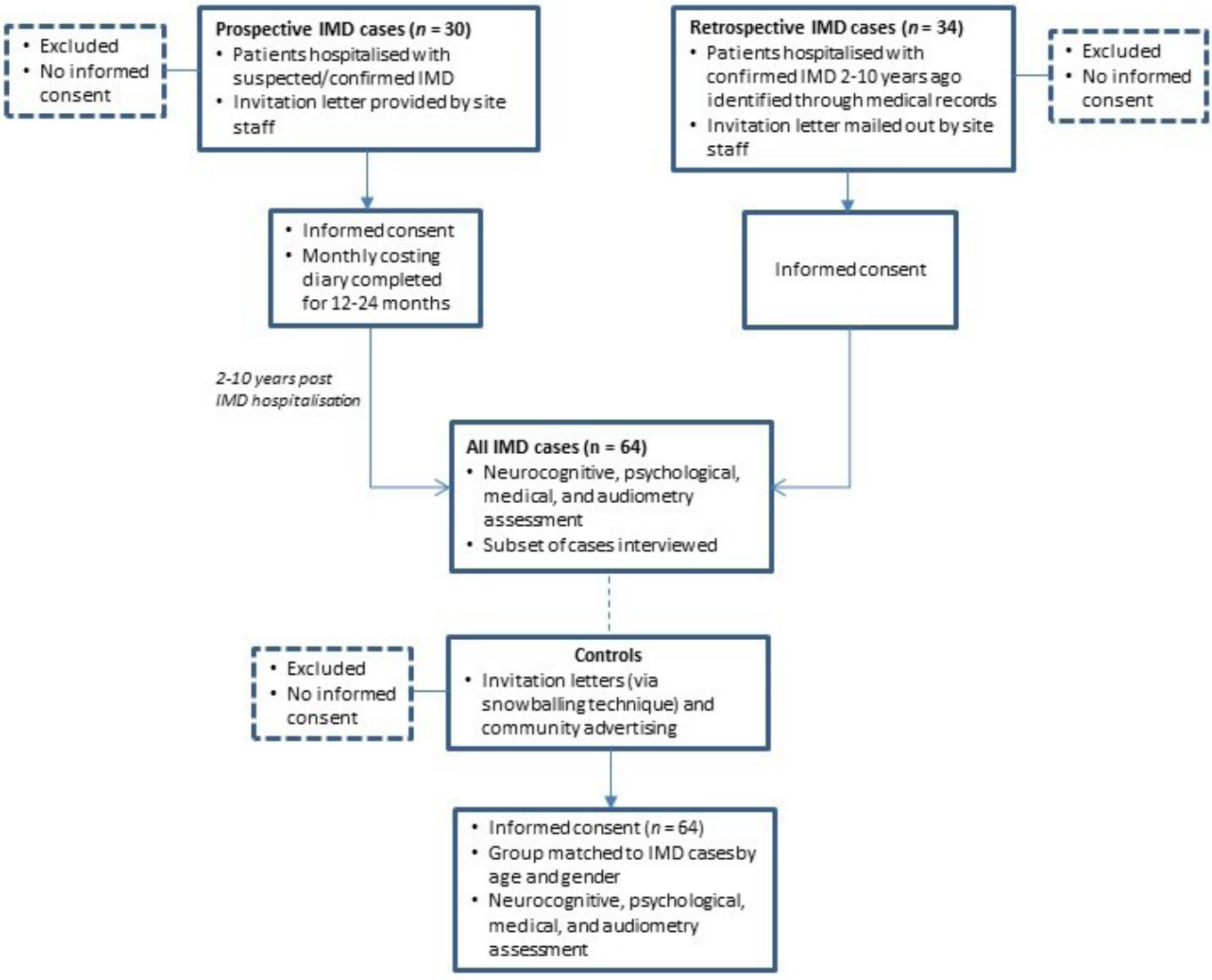

Figure1 Adolescent MENingococcal Disease (AMEND) study recruitment flow chart. IMD, invasive meningococcal disease.

disclose their case/control status to the psychologist. On completion of all outcome measures participants will be provided with a AUD$150 voucher to cover any costs associated with travelling and their time in completing the assessments.

Primary outcome measures

Intellectual functioning will be measured by the Full Scale IQ score obtained from the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV),[30] a widely used and standardised test of intelligence.

QoL will be measured by the overall multiattribute health utility score obtained from the Health Utilities Index Mark 3 (HUI3)–15Q self-report.[31] The HUI3 consists of 15 items assessing the following domains: vision, hearing, speech, cognition, pain, emotion, ambulation and dexterity. The HUI has been used in previous IMD studies including children (16 years) approximately 5 months post-IMD (group B)[32] and survivors of meningococcal septic shock.[33]

Secondary outcome measures

Neurocognitive and psychological outcomes

Standardised psychometric measures assessing academic achievement, executive and memory (verbal and visual) functioning of all participants will be administered by a psychologist (table 1). Questionnaires assessing attention, executive functioning, behaviour and psychological problems will also be completed by participants and/or parents (table 1). Participants will undergo a structured diagnostic interview conducted by the site psychologist to screen for psychiatric disorders (table 1). On completion, all participants will receive a follow-up phone call/feedback from the psychologist and a brief summary report of their neurocognitive results.

Medical and audiometry examination

Each participant will undergo a full medical examination conducted by the site physician using the International Classification of Functioning, Disability and Health tool to assess for the presence of body function/structure

Table 1 Neurocognitive and psychological outcomes

Domain	Test	Age range
Intelligence	Wechsler Adult Intelligence Scale—Fourth Edition[30]	16–90 years
Academic achievement	Wechsler Individual Achievement Test—Second Edition[53] subtests: Reading, Spelling, Maths Reasoning, Reading Comprehension	4 years adults
Executive functioning	Delis-Kaplan Executive Function System[54] subtests: Trail Making Test, Color Word Interference Test, Verbal Fluency Test, Sorting Test	8–89 years
	Behavior Rating Inventory of Executive Function (BRIEF)[55]—parent	5–18 years
	BRIEF[55] adolescent self-report	11–18 years
	BRIEF[55] adult self-report	≥18 years
Memory	Wide Range Assessment of Memory and Learning, Second Edition[56] subtests: Verbal Learning and Design Memory	5–90 years
Psychiatric screening	Mini International Neuropsychiatric Interview (M.I.N.I. 6.0 kids)[57]	6–17 years
	M.I.N.I 6.0 adult[57]	≥18 years
	Depression Anxiety Stress Scales (DASS)[58]	>14 years
Attention Deficit Hyperactivity Disorder (ADHD) and problem behaviour	Conners Third Edition (Conners 3)[59]—parent full length	6–18 years
	Conners 3[59]—self-report full length	8–18 years
	Conners Adult ADHD Rating Scales (CAARS)[60] long form: self-report	≥18 years
	CAARS[60] long form: observer	≥18 years

impairments, restrictions in physical activities and participation.[34] A pure tone audiometry will be conducted and hearing will be classified as no impairment (0) to profound (5).[35]

QOL and carer experience

All participants will complete the the 5-level EQ-5D (EQ-5D-5L) to measure their health status, which will be used to calculate quality-adjusted life years lost (table 2). For those participants with a disability, the primary caregiver and other family members living in the same household will be invited to complete questionnaires assessing their well-being and carer experience (table 2). All questionnaires shown in table 2 have been used in previous meningococcal studies.[32 33 36–40]

Socioeconomic status

Socioeconomic status (SES) of participants will be estimated using the index of relative socioeconomic advantage and disadvantage, which ranks geographical areas in terms of their socioeconomic advantage and disadvantage.[41] The lowest 10% of areas are ranked a decile of 1 and the highest 10% are ranked a decile of 10.

Clinical information for IMD cases only

A standardised data collection sheet will be completed to capture information on clinical disease, management, complications, outcomes and sequelae for IMD cases. Data on age, gender, indigenous status, comorbidities, social demographic (eg, residence areas, postcodes), length of admission and outcome will be recorded by medical or nursing staff at each participating hospital. In addition, signed informed consent will be obtained from participants to access health databases including Medicare (publicly funded universal healthcare system); the Australian Government Pharmaceutical Benefits Scheme (PBS)[42] national programme, which subsidises the cost of a wide range of prescribed medicines for all Australians; and general practitioner/specialist clinical records. IMD cases recruited prospectively will be asked to complete monthly diary cards for at least 12 months and up to 24

Table 2 Quality of life (QoL) and carer questionnaires

Domain	Test	Age range	Completed by
Overall QoL	ICEpop CAPability measure for adults[61]	≥18 years	Parent and other family members
Care-related QoL	Carer Experience Scale (6 questions)[62]	≥18 years	Primary caregiver
Health-related QoL	Health Utilities Index Mark 3–15Q[31] domains: vision, hearing, speech, cognition, pain, emotion, ambulation and dexterity.	≥15 years	Participant
Health status to calculate quality-adjusted life years lost	Five level EQ-5D[63] (EQ-5D-5L) domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.	≥15 years	Participant

months depending on the time of enrolment to obtain details of any medical follow-up and progress in relation to sequelae and associated direct non-healthcare and indirect costs. The site study coordinator will phone/email participants monthly to check that the diary is being completed and returned to the site investigator via provided self-addressed envelopes/email.

Qualitative data

Semistructured interviews for IMD cases only

To obtain more detailed information about the impact of IMD, in-depth interviews on a subset of IMD cases will be conducted until thematic saturation. The interview will be semistructured and consist of a series of questions (eg, can you tell me about the symptoms and treatment you received for IMD; does IMD impact on your daily life, if yes, how); however, the interviewer will be trained in techniques to allow the interview to be flexible, to generate new questions during the interview, to probe for details and discuss issues that arise during the interview. Interviews will be completed face to face, although if this is not possible, they will be performed over the phone. Interviews will be completed 2–10 years postdiagnosis of IMD and audio recorded.

Adverse event monitoring

The study-related adverse event (AE) reporting period commences when the participant provides informed consent and continues until study participation is complete. An expected AE of the study is that a participant becomes distressed when completing the assessments and/or interview (IMD cases only). All AEs will be reported to the relevant Human Research Ethics Committee. For all AEs, the site investigator will be required to assess and record the causal relationship. Sufficient information will be obtained by the site investigator to determine the causality of each AE. The investigator will be required to follow up AEs until the event and/or its sequelae resolve or stabilise at a level acceptable to the investigator. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that any study processes caused or contributed to an AE.

Sample size

The primary outcomes are Full Scale IQ (WAIS-IV) and QoL (HUI-3 overall) scores. In a large IMD case–control study of children, there was a difference of 7.5 Full Scale IQ points between cases and controls matched by age and gender,[7] an estimated medium effect size (Cohen's d=0.50). In the same study,[7] an unmatched comparison of IMD cases to controls indicated a difference of 7.4 Full Scale IQ points also representing a medium effect size. In a study investigating the QoL of mainly childhood survivors (median age 14.5 years, age range 5–31 years) approximately 10 years postintensive care discharge for IMD, HUI-3 overall scores were significantly lower by 0.11 when compared with normative data,[33] representing a medium effect size (Cohen's d=0.56). Therefore, based on these previous studies, we have estimated a medium effect size (Cohen's d=0.50) between cases and controls. To detect a medium effect size between groups using an independent t-test, with 80% power, two-tailed significance of 0.05, 64 (+10% for lost to follow-up) participants are required in each group.[43]

Statistical analysis

Quantitative analyses

Descriptive statistics will be reported. Continuous variables will be compared between cases and controls using independent t-tests. Categorical variables will be compared between groups using tests of X^2 or ORs (95% CI). However, if any significant confounders (eg, age, gender, SES) are identified then an adjusted analysis using analysis of covariance and adjusted ORs (95% CI) will be conducted. All tests will be two tailed with the Benjamini-Hochberg method applied to reduce the False Discovery Rate (FDR) by controlling for multiple hypotheses testing.[44] For continuous variables, effect sizes (Cohen's d) will also be calculated.

For neurocognitive outcomes, the level of impairment will also be classified by the number of SD below the normative mean (mild: 1.0–1.9 SD below, moderate: 2.0–2.9 SD and severe:≥3.0 SD). Differences in medical examination and audiometry findings including the type and frequency of hearing impairments in cases and controls will be reported descriptively. Definitions of major and minor sequelae will be classified using WHO Global Burden of Disease[45] and a systematic review/meta-analysis of disabling sequelae from bacterial meningitis.[5] This classification of sequelae was used in a previous IMD study.[7] Major sequelae are defined as cognitive impairment (Full Scale <70), bilateral sensorineural hearing loss (≥40 dB), seizures (any type), disabling motor impairment (eg, amputation of part of a limb or more than one digit), significant visual loss or major communication impairment (unintelligible speech or cannot understand speech). Minor sequelae are defined as other cognitive, hearing, motor, visual, communication impairments and psychological disorders. ORs (95% CI) for the occurrence any minor, any major and all sequelae will be calculated.

An exploratory multiple linear regression to identify predictors of QoL of IMD participants will be conducted. Potential predictors include Full Scale IQ, time from IMD hospitalisation to study assessment, presence/absence of major sequelae and psychological functioning. If there are sufficient serogroup B IMD cases, their outcomes will be compared with non-serogroup B IMD cases using the same analyses as mentioned above for continuous and categorical variables.

In addition, to assess the impact of potential correlation between participants in the same hospital, we will conduct a sensitivity analysis to determine the effect of any potential clustering on the outcomes and the conclusions of the study and to estimate correlation within clusters, for example, using generalised estimating equations.

Health economic analyses

We anticipate obtaining consent to access health databases including Medicare and the PBS from all IMD cases enrolled (n=64). Direct medical costs will be based on routinely collected data describing the type and frequency of inpatient separations obtained from state health databases for hospital admissions. The cost of outpatient services (eg, visits to primary care physicians) and pharmaceuticals will be derived from Medicare including PBS.

Patient's monthly diary cards completed by prospective patients (estimated n=30) will be used to estimate other direct costs, such as out of pocket costs, health services, which are not covered by Medicare (eg, ambulance services) and copayments (eg, on pharmaceuticals), as well as direct non-medical costs, such as travel costs and time spent travelling to medical appointments, and indirect costs due to cessation or reduction of workforce activity (productivity).

A micro-costing (bottom–up) approach, which provides detailed cost information, will be used to estimate costs associated with IMD from the healthcare system and societal perspectives. A costing model will be developed to estimate lifetime costs associated with IMD, taking into account different discount rates (ie, annual rates of 3.5% or 5%).[46] By using the micro-costing approach, resources used at the individual level will be assessed and costs of individual patients will be aggregated. The micro-costing approach reflects the true costs to deliver care to the individual patient .[47] The bottom–up approach, which highly depends on availability of data on treatment costs or productivity losses, can provide more detailed information for analysis and stratification than top–down (population-based) approach. By using the top–down method, total healthcare costs would be disaggregated, and a relevant portion of the total costs would be allocated to a specific disease.[47] A decision analytic model (eg, Markov model with yearly cycles) will be built. The model structure will include health states and transitions between them representing the type of care required with death as an absorbing state. Relevant cost estimates per cycle will then be attached to states included in the model. A hypothetical birth cohort will be followed over a 100-year time horizon. Health states, probabilities of health states and costing parameters will be obtained from a variety of sources including the present study and/or published literature. The best available evidence will be used to inform model structure and inputs.

In addition to reporting the base case analysis, the model developed will be used to undertake sensitivity analysis over a range of uncertain parameters to inform the likely impact of using alternative values.

Qualitative analyses

Interviews will be transcribed verbatim and analysed using iterative thematic analysis techniques to enable an understanding of the participant's experiences of IMD in particular, details of their hospitalisation and treatment, the impact of IMD on their daily life after being discharged and currently and details of any support (eg, social, healthcare professionals) that they have received. Similar to the methods used previously,[48] interview transcripts will be subjected to coding by one investigator. A second investigator will code transcripts independently, and then both investigators will meet to discuss their analysis. This iterative process will allow movement between data collection and analysis as codes are interpreted and themes generated. Transcripts will be read and reread and initial codes assigned based on the language used by the participants themselves. Discussion between researchers, coding notes and memos will be used to ensure consistency in the coding framework. Initial themes will be identified by discussion between the researchers and matrixes, grids and tables will be used to visualise the relationship between the themes and the experiences of each of the participants. Qualitative findings will be used to complement[49] quantitative findings. For example, major sequelae may impact on the QoL participants and interviews will provide further richness and understanding on how the sequelae impacts on their life.

Patient and public involvement

The research question was developed in response to policy advisors identification of the evidence gap in understanding the long-term impact of meningococcal disease on survivors. Assistance in study processes has been provided by meningococcal and meningitis support groups in Australia.

Data management and confidentiality

Identifying documents will be maintained at each participating site in locked cabinets and offices. Data management will be coordinated and overseen by the site principal investigator (PI) at the Women's and Children's Health Network, Adelaide. Quantitative data collected during the study will be entered by site staff into an online (Research Electronic Data Capture [REDcap]) database in a reidentifiable manner. The electronic database is username and password protected and located on the server at the University of Adelaide. Except for the University of Adelaide staff who will be analysing the data, all other site investigators can only access and view data from their own site. Following data analysis, the data will be deleted from REDcap and a deidentified password-protected dataset will be stored on the University of Adelaide server and deleted after 30 years.

Reidentifiable data are identifiable only at the recruiting study site where a master participant code list will be retained by the site investigator. The list will be stored electronically on their computer that is password protected and only accessible to them. Information published from this study will not identify any participants involved in this study.

Ethics and dissemination

Participants who are at least 18 years of age will be approached and the study discussed with them. If they

agree to participate, an information sheet will be provided with an opportunity to discuss the study with the study team and a consent form will be signed by the participant. If the participant is 17 years of age or less, assent will be obtained and the parent/guardian will provide informed signed consent. A second consent to release of Medicare and/or PBS claims information form is also required to be signed prior to release of information from the Department of Human Services. Detection of neurocognitive impairments and/or elevated psychological symptoms (eg, symptoms of depression) may be upsetting to participants and their families. We will facilitate referral for follow-up with their family physician and/or psychologist where appropriate with consent of the participant.

The results will be disseminated via peer-reviewed publications and conference presentations, and a summary of the findings will be provided to study participants, the wider community and meningococcal support foundations. The results may also be reported on websites (eg, hospitals, foundations) and in the media including television, radio and print media.

Significance

This study is being conducted at a time when, increasingly, public health strategies are subject to consideration of the relative economic cost of the proposed strategy. Our study will contribute robust data to assess the societal cost of disability from infectious disease by examining the most common infectious cause of death in AYA in Australia, IMD.

The strengths of our study include the use of both objective and subjective standardised measures to determine the long-term outcomes and disability experienced by IMD survivors, national recruitment of IMD cases and only those who are AYA. Some IMD survivors may be less likely to have resources to attend study locations and/or may come from rural settings and have lower SES. However, we have attempted to ameliorate any participation bias by providing travel reimbursement for participants. For patients with severe disabilities, their health conditions and inconvenience may prevent participation in the study.

This national study will include data from four states of Australia. These findings will have global significance as other countries are currently considering introduction of meningococcal vaccines in their national immunisation programmes. The UK Joint Committee on Vaccination and Immunisation initially concluded that an infant MenB vaccine programme would not be cost-effective and recommended not funding Men B immunisation.[18] However, negotiations with the manufacturer resulted in an agreed price and a programme commenced in 2015.[21] In Australia, the Pharmaceutical Benefits Advisory Committee rejected including MenB vaccine on the publicly funded national immunisation schedule on three occasions (2013–2015) due to uncertainties and assumptions used in the cost-effectiveness model.[46 50–52] As only limited data exist globally on the long-term burden of IMD our study will provide comprehensive data on the impact of IMD on AYA survivors, which can further inform cost-effectiveness estimates, particularly for adolescent programme.

CONCLUSION

Australia has limited outcome data for patients who survive IMD and little is known about the impact the disease has on the life of AYA survivors. The results from this study will provide the comprehensive data required to understand the impact of IMD in young people, as well as to assess the long-term health and financial implications for the individual, their families and the healthcare system. These data are essential for cost-effectiveness estimates for countries considering the introduction of this uncommon but potentially life-threatening and disabling infection.

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Competing interests HM is supported by an NHMRC CDF APP1084951 and is a member of the Australian Technical Advisory Group on Immunisation, Australian Government. HM is an investigator on vaccine trials sponsored by Industry (GSK, Novavax, Pfizer). HM and MM's institution receives funding for investigator-led studies from Industry (Pfizer, GSK). HM and MM receive no personal payments from Industry. CCB is supported by an NHMRC CDF APP1111596 and is a member of the Australian Technical Advisory Group on Immunisation, Australian Government. PR is an investigator on vaccine trials sponsored by Industry (GSK, Novavax, Pfizer). PR's institution receives funding for investigator-led studies from Industry (Pfizer, GSK, CSL). PR has been a member of scientific vaccine advisory boards for Industry (Pfizer, GSK, Sanofi) but has not received any personal payments from Industry. DG

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