BMJ Open

The AMEND Study Protocol: A case-control study to assess the long-term impact of invasive meningococcal disease in Australian adolescents and young adults

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032583
Article Type:	Protocol
Date Submitted by the Author:	26-Jun-2019
Complete List of Authors:	Marshall, Helen; University of Adelaide, Robinson Research Institute and Adelaide Medical School; Women's and Children's Health Network, Vaccinology and Immunology Research Trials Unit McMillan, Mark; The University of Adelaide, Robinson Research Institute and Adelaide Medical School; Women's and Children's Health Network, Vaccinology and Immunology Research Trials Unit Wang, Bing; The University of Adelaide, Robinson Research Institute and Adelaide Medical School; Women's and Children's Health Network, Vaccinology and Immunology Research Trials Unit Booy, Robert; The Children's Hospital at Westmead, The Discipline of Child and Adolescent Health; The Children's Hospital at Westmead, National Centre for Immunisation Research and Surveillance (NCIRS) Afzali , Hossein; Univeristy of Adelaide, School of Public Health Buttery, Jim; Royal Children's Hospital, Department of Paediatrics Blyth, Christopher C.; Perth Children's Hospital, Department of Infectious Diseases Richmond, Peter; University of Western Australia and Wesfarmers centre of Vaccines and Infectious Diseases, Telethon Kid's Institute, School of Medicine Shaw, David; SA Health, Infectious Diseases Service Gordon, David; Flinders Medical Centre, Microbiology and Infectious Diseases Barton, Belinda; The Children's Hospital at Westmead, Children's Hosptial Education Research Institute
Keywords:	meningococcal disease, sequelae, neurocognitive, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, adolescents, young adults

The AMEND Study Protocol: A case-control study to assess the long-term impact of invasive meningococcal disease in Australian adolescents and young adults

Authors: Helen S Marshall [1,2], Mark McMillan [1,2] , Bing Wang [1,2], Robert Booy[3,4], Hossein Haji Ali Afzali[5], Jim Buttery[6], Christopher C Blyth[7], Peter Richmond[8], David Shaw[9], David L Gordon[10], Belinda Barton[11]

Corresponding Author: Helen Marshall, Women's and Children's Hospital, 72 King William Rd, North Adelaide, 5006, SA, Australia T: +61 8 8161 8115 Fax: +61 8 8161 7031
E: *helen.marshall@adelaide.edu.au*

Affiliations:

1. Vaccinology and Immunology Research Trials Unit, Women's and Children's Health Network, Adelaide, South Australia, Australia
2. Robinson Research Institute and Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
3. The Discipline of Child and Adolescent Health, the Children's Hospital at Westmead Clinical School, The University of Sydney Medical School, Australia.
4. National Centre for Immunisation Research and Surveillance (NCIRS), The Children's Hospital at Westmead, NSW, Australia
5. School of Public Health, University of Adelaide, Adelaide, South Australia, Australia
6. Department of Paediatrics, Royal Children's Hospital, Victoria, Australia
7. Department of Infectious Diseases, Perth Children's Hospital, Western Australia
8. School of Medicine, University of Western Australia and Wesfarmers centre of Vaccines and Infectious Diseases, Telethon Kid's Institute, Perth, Western Australia
9. Infectious Diseases Service, Central Health Service, South Australia, Australia
10. Microbiology and Infectious Diseases, SA Pathology, Flinders Medical Centre, Bedford Park, South Australia, Australia
11. Children's Hospital Education Research Institute, The Children's Hospital at Westmead, Sydney, Australia

Keywords: meningococcal disease, sequelae, neurocognitive, health economics, immunisation programs, adolescents, young adults

Sponsor: The University of Adelaide

Funding: Pfizer

Word Count: 4379 (excluding title page, abstract, tables, strengths and limitations, acknowledgements, contributions and references). In response to reviewer feedback, we have provided more detail. This has taken us 379 words over the limit.

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 programs 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 post hospitalisation 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 odds ratio, or if any significant confounders are identified, adjusted analyses (ANCOVA or adjusted odds ratio) 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 study has been approved by the Women's and Children's Health Network Human Research Ethics Committee HREC/14/WCHN/024. Results will be disseminated via peer-reviewed publications, conference presentations, study participants, and meningococcal and meningitis foundations.

Trial registration

Clincialtrials.gov:NCT03798574

Strengths and limitations of this study

- Generation of new evidence to inform vaccination policy for protecting adolescents and young adults from 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 generalizability of the data to Australia and similar countries like New Zealand, Canada, United Kingdom and the United States.
- 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 provides 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 can cause permanent sequelae which may lead to significant disability in approximately 7.2% (4.3–11.2%) of survivors.[4]

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 and long term post IMD and have been reported in child and adult survivors.[5 6] 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 a third of IMD cases (36%) had one or more deficits in physical, cognitive, and psychological functioning versus 15% of controls.[6] However while these deficits were relatively common, their impact on the QoL of children was not examined.

Whilst meningococcal disease affects all age groups, the incidence of IMD peaks in the 0 to 4 year, and 15 to 25 year age groups in some countries, including Australia.[7-9] To date few studies have examined the long term impact of IMD on adolescents and young adults (AYA) aged 15 to 25 years old 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,[10] 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.[11 12] Results from a study of young adult males (18 to 24 years old at the time of IMD) conducted over 30 years ago indicated that 3 to 15 years post IMD, survivors reported significantly more symptoms of possible sequelae compared to the control group (61% vs 20%).[13] In

addition, around 30% reported that the disease had affected their education or working capacity.[13] In another study adolescents (15 – 19 years old at time of IMD) who were followed up 18 to 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 to matched controls.[5] Adolescent survivors also reported significantly poorer physical and mental health (i.e. depression) as well as QoL when compared to controls. Disabling physical sequelae were identified in 57% of survivors and 5% required amputations.[5]

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.[14] 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.[14] Further studies of indirect costs of IMD are imperative to estimate the total financial burden of IMD.

The health economic evaluation of meningococcal vaccine programs has identified that further data on long term sequelae would be beneficial.[15] For vaccines against uncommon diseases like IMD, the results of health economic evaluations can vary significantly depending on the parameter values used (e.g. treatment costs, QoL losses of IMD), or on the basis of expert opinions.[16 17] 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 programs difficult.[18]

Although meningococcal vaccines are licensed in many countries, they are not necessarily publicly funded due to unknown or unfavourable cost-effectiveness analyses.[19] Only the UK has introduced a national funded MenB vaccine program which is provided for infants. Due to increasing incidence of meningococcal W IMD cases in the UK a funded MenACWY vaccine program has been introduced.[20]

In Australia a MenACWY program has been introduced for infants at 1 year of age and will be funded for adolescents 14-19 years of age from 2019.[21] However none of these programs provide 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 program, but detailed and contemporary data on the clinical benefit and long-term costs are not available, particularly for AYA.[22]

Findings from this study will assist in more robust data to inform policy as to whether meningococcal vaccines should be included in routine immunisation programs. 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.[23] Such studies can also be used to aid policy-makers to estimate cost savings and medical benefits in economic evaluations of health care interventions and to inform public health policies such as funding priorities and immunisation programs.[24-26]

In summary, survivors of IMD experience a range of mild to severe sequelae that impact upon 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 i) assessing the impact of IMD on

neurocognitive (academic achievement, executive functioning, memory), psychological and physical functioning; ii) estimating the lifetime costs associated with survival following IMD and iii) 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 multi-centre, case-control, mixed-methods 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).

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 and will also access hospital separation data to identify any admissions coded with International Classification of Diseases (ICD) 10-A39.0 to A39.9.[27] After a diagnosis of IMD has been confirmed by PCR or culture 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 hospitalized 2 to 10 years ago with confirmed IMD will be identified from discharge coding and/or hospital medical records. After a diagnosis of IMD has been confirmed by PCR or culture 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 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.[28] 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 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[27] or ICD 9-036. All IMD cases must have a confirmed infection (PCR or culture) with *N. meningitidis* of any serogroup which will be verified by the site nurse or doctor.
- IMD cases must be aged 15 years to 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 to 10 years at the time of study assessments (retrospective).
- Controls will be aged 17 to 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 to 10 years post IMD.

Exclusion criteria

- Individuals who are not fluent with the English language.
- 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 IMD cases, all assessments will be conducted 2 to 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 disclose their case/control status to the psychologist. On completion of all outcome measures participants will be provided with a $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),[29] a widely used and standardized test of intelligence.

QoL will be measured by the overall multi-attribute health utility score obtained from the Health Utilities Index Mark 3 (HUI3)-15Q self-report.[30] 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)[31] and survivors of meningococcal septic shock.[32]

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). Self-

reported questionnaires assessing attention, executive functioning, behavior and psychological problems will also be completed by participants (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.

Table 1 Neurocognitive and psychological outcomes

Domain	Test	Age Range
Intelligence	Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV)[29]	16 to 90 years
Academic Achievement	Wechsler Individual Achievement Test - Second Edition (WIAT-II)[33] subtests: reading, spelling, maths reasoning, reading comprehension	4 years - adults
Executive Functioning	Delis–Kaplan Executive Function System (D-KEFS)[34] subtests: Trail Making Test, Color Word Interference Test, Verbal Fluency Test, Sorting Test	8 to 89 years
	Behavior Rating Inventory of Executive Function (BRIEF)[35] – parent	5-18 years
	BRIEF Adolescent self-report	11-18 years
	Behavior Rating Inventory of Executive Function - Adult self-report	≥ 18 years
Memory	Wide Range Assessment of Memory and Learning, Second Edition (WRAML2)[36] subtests: Verbal Learning and Design Memory	5-90 years
Psychiatric screening	Mini International Neuropsychiatric Interview (M.I.N.I. 6.0 kids)[37]	6 -17 years
	M.I.N.I 6.0 Adult[37]	≥ 18 years
	Depression Anxiety Stress Scales (DASS)[38]	>14 years
ADHD & problem Behavior	Conners Third Edition (Conners 3)[39] - Parent Full-length	6-18 years
	Conners 3[39] – Self-report Full length	8-18 years
	Conners Adult ADHD Rating Scales (CAARS)[40] Long Form: Self-Report	≥ 18 years
	CAARS Long Form: Observer	≥ 18 years

Medical and audiometry examination

Each participant will undergo a full medical examination conducted by the site physician including a health and disability assessment using the International Classification of Functioning, Disability and Health (ICF) tool[41] and pure tone audiometry.

Quality of life (QoL) and carer experience

All participants will complete the EQ-5D-5L to measure their health status, which will be used to calculate quality adjusted life years (QALYS) 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. [31 32 42-46]

Table 2 Quality of life (QoL) and carer questionnaires

Domain	Test	Age Range	Completed by
Overall quality of Life	ICEpop CAPability measure for adults (ICECAP-A)[47]	≥ 18 years	Parent and other family members
Care-related quality of life	Carer Experience Scale (6 questions)[48]	≥ 18 years	Primary caregiver
Health-related quality of life	Health Utilities Index Mark 3 (HUI3)-15Q[30] Domains: vision, hearing, speech, cognition, pain, emotion, ambulation and dexterity.	≥ 15 years	Participant
Health status to calculate quality adjusted life years (QALYS) lost	EQ-5D-5L[49] (5 questions) Domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.	≥ 15 years	Participant

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 demography (e.g. 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 Pharmaceutical Benefits Scheme (PBS) that subsidises a wide range of medicines for all Australians, and GP/specialist clinical records. IMD cases recruited prospectively will be asked to complete monthly diary cards for at least

12 months and up to 24 months depending upon 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

Semi-structured 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 semi-structured and consist of a series of questions (e.g. 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 to 10 years post diagnosis of IMD and audio recorded.

Adverse event monitoring

The study related serious adverse event (SAE) reporting period commences when the participant provides informed consent and continues until study participation is complete. All SAEs will be reported to the relevant Human Research Ethics Committee. For all SAEs, 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 SAE. The investigator will be required to follow-up SAEs until the event and/or its sequelae resolve or stabilize 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 adverse event.

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,[6] an estimated medium effect size (Cohen's *d* = 0.50). In the same study,[6] 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 post intensive care discharge for IMD, HUI-3 overall scores were significantly lower by 0.11 when compared to normative data,[32] 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 loss to follow-up) participants are required in each group.[50]

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 chi-squared or odds ratio (95% CI). However if any significant confounders are identified then an adjusted analysis using ANCOVA and adjusted odds ratio (95% CI) will be conducted. All tests will be two-tailed with the Benjamini-Hochberg method applied to control the False Discovery Rate. For continuous variables effect sizes (Cohen's *d*) will also be calculated.

For neurocognitive outcomes, level of impairment will also be classified by the number of standard deviations (SD) below the normative mean (mild: 1.0-1.9SD below, moderate: 2.0-2.9SD and severe: ≥3.0SD).

Differences in medical examination findings including audiometry assessments of cases and controls will be reported descriptively. Definitions of major and minor sequelae will be classified using the World Health Organization Global Burden of Disease[51] that has been used in previous IMD studies.[4 6] Odds ratio (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 since disease, presence/absence of major sequelae and psychological functioning. If there are sufficient serogroup B IMD cases, their outcomes will be compared to 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 assess the impact of any potential clustering on the outcomes and the conclusions of the study and to estimate correlation within clusters, for example using generalized 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 (e.g. visits to primary care physicians) and pharmaceuticals will be derived from Medicare including PBS.

Patient monthly diary cards and questionnaires 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 (e.g. ambulance services) and co-payments (e.g. 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 (i.e annual rates of 3.5% or 5%).[52] A decision analytic model (e.g. 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 (e.g. social, healthcare professionals) that they have received. Similar to methods used previously,[53] 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 re-read 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.

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 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 (REDcap)database in a re-identifiable manner. The electronic database is username and password-protected and located on the server at the University of Adelaide. Except for 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 de-identified password protected dataset will be stored on the University of Adelaide server and deleted after 30 years.

Re-identifiable data is 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 which 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:

The study has been approved by the Women's and Children's Health Network Human Research Ethics Committee. Governance and ethics approval has also been obtained at all other affiliated sites. 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 (e.g. 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.

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. Results may also be reported 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 standardized 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 socioeconomic status. 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 study is nationally representative as it will include data from four states in Australia. These findings will have global significance as other countries are currently considering introduction of meningococcal vaccines in their national immunisation programmes. The United Kingdom Joint Committee on Vaccination and Immunisation initially concluded that an infant MenB vaccine program would not be cost-effective and recommended not funding Men B immunisation.[17] However, negotiations with the manufacturer resulted in an agreed price and a program commenced in 2015.[20] 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.[52 54-56] 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 programs.

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. 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.

REFERENCES

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

2 Chang Q, Tzeng YL, Stephens DS. Meningococcal disease: changes in epidemiology and prevention. *Clin Epidemiol* 2012;**4**:237-45.

3 Jafri RZ, Ali A, Messonnier NE et al. Global epidemiology of invasive meningococcal disease. *Popul Health Metr* 2013;**11**:17.

4 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**:317-28.

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

6 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;**11**:774-83.

7 Lahra M, Enriquez R. Australian Meningococcal Surveillance Programme annual report, 2014, Canberra, Australia: Australian Government Department of Health 2016, http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-pubs-annlrpt-menganrep.htm (Accessed 12th July 2018).

8 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**:197-207.

9 Pelton SI. The Global Evolution of Meningococcal Epidemiology Following the Introduction of Meningococcal Vaccines. *J Adolesc Health* 2016;**59**:S3-S11.

10 Patton GC, Sawyer SM, Santelli JS et al. Our future: a Lancet commission on adolescent health and wellbeing. *Lancet* 2016;**387**:2423-2478.

11 Keshavan MS, Giedd J, Lau JY, Lewis DA, Paus T. Changes in the adolescent brain and the pathophysiology of psychotic disorders. *Lancet Psychiatry* 2014;**1**:549-58.

12 Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev* 2000;**24**:417-63.

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

14 Wang B, Santoreneos R, Afzali H, Giles L, Marshall H. Costs of Invasive Meningococcal Disease: A Global Systematic Review. *PharmacoEconomics* 2018.

15 Borrow R, Alarcon P, Carlos J et al. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. *Expert Rev Vaccines* 2017;**16**:313-328.

16 Jit M, Hutubessy R. Methodological Challenges to Economic Evaluations of Vaccines: Is a Common Approach Still Possible? *Appl Health Econ Health Policy* 2016;**14**:245-52.

17 Joint Committee on Vaccination and Immunisation (JCVI). JCVI interim position statement on use of Bexsero® meningococcal B vaccine in the UK 2013 UK: Department of Health and Social Care 2013, https://www.gov.uk/government/publications/jcvi-interim-position-statement-on-the-use-of-bexsero-meningococcal-b-vaccine-in-the-uk (Accessed 12th July 2018).

18 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**:280-8.

19 European Centre for Disease Prevention and Control. Expert opinion on the introduction of the meningococcal B (4CMenB) vaccine in the EU/EEA, Stockholm: ECDC 2017, https://ecdc.europa.eu/en/publications-data/expert-opinion-introduction-meningococcal-b-4cmenb-vaccine-eueea (Accessed 21st December 2018).

20 Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. Enter B and W: two new meningococcal vaccine programmes launched. *Arch Dis Child* 2016;**101**:91-5.

21 Australian Technical Advisory Group on Immunisation. National Immunisation Program Schedule, Canberra: Australian Government Department of Health 2018, https://beta.health.gov.au/health-topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule (Accessed 7th January 2019).

22 Pharmaceutical Benefits Advisory Committee. Meningococcal polysaccharide conjugate vaccine serogroups A, C, W-135 and Y(adolescents): Pre-filled syringe, 0.5mL; Nimenrix® Pharmaceutical Benefits Scheme, Canberra: Department of Health, Australian Government 2018, http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-03/Meningococcal-polysaccharide-conjugate-vaccine-adolescents-psd-march-2018. (Accessed 21st December 2018).

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

24 Byford S, Torgerson DJ, Raftery J. Economic note: cost of illness studies. *BMJ* 2000;**320**:1335.

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

26 Chisholm D, Saxena S, Van Ommeren M. Dollars, DALYs and decisions: economic aspects of the mental health system, Geneva: World Health Organization 2006, http://apps.who.int/iris/handle/10665/43574 (Accessed 12th July 2018).

27 Classifications, Geneva: World Health Organisation 2018, https://www.who.int/classifications/icd/en/ (Accessed 12th December 2018).

28 The SAGE Encyclopedia of Social Science Research Methods, Thousand Oaks, California: Sage Publications, Inc. 2004, http://dx.doi.org/10.4135/9781412950589 (Accessed 12th December 2018).

29 Wechsler D. Wechsler Adult Intelligence Scale-3rd Edition (WAIS-IV) Australian and New Zealand adaptation. Sydney, NSW: Pearson, 2008.

30 Furlong WJ, Feeny DH, Torrance GW. Health utilities index® mark 2 and mark 3 (hui2/3) 15-item questionnaire for Self-administered, self-assessed "four week" health status assessment. Dundas ON Canada: Health Utilities Inc, 2016.

31 Kennedy ITR, van Hoek AJ, Ribeiro S et al. Short-term changes in the health state of children with group B meningococcal disease: A prospective, national cohort study. *PLoS One* 2017;**12**:e0177082.

32 Buysse CM, Raat H, Hazelzet JA et al. Long-term health status in childhood survivors of meningococcal septic shock. *Arch Pediatr Adolesc Med* 2008;**162**:1036-41.

33 Wechsler D. Wechsler Individual Achievement Test- Second Edition (WIAT-II). London, UK: Psychological Corporation., 2005.

34 Delis D, C Kaplan E, Kramer JH. Delis-Kaplan Executive Function System. San Antonio, TX: The Psychological Corporation, 2001.

35 Gioia G, Isquith P, Guy S, Kenworthy L. Behavior Rating Inventory of Executive Function (BRIEF). Lutz, Florida: Psychological Assessment Resources, 2000.

36 Sheslow D, Adams W. Wide Range Assessment of Memory and Learning, Second Edition (WRAML2). Bloomington: Pearson, 2003.

37 Sheehan DV, Lecrubier Y, Sheehan KH et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;**59 Suppl 20**:22-33;quiz 34-57.

38 Psychology Foundation of Australia. Depression Anxiety Stress Scales (DASS), UNSW: Psychology Department, UNSW 2014, http://www2.psy.unsw.edu.au/dass/ (Accessed 12th December 2018).

39 Conners K ED, Sparrow E,. Conners 3rd edition (Conners) Manual. Canada: Multi-Health Systems Inc, 2009.

40 Conners K ED, Sparrow E, . Conners' Adult ADHD Rating Scales. Canada: Multi-Health Systems Inc, 2002.

41 Kostanjsek N. Use of The International Classification of Functioning, Disability and Health (ICF) as a conceptual framework and common language for disability statistics and health information systems. *BMC Public Health* 2011;**11**:S3-S3.

42 Al-Janabi H, Manca A, Coast J. Predicting carer health effects for use in economic evaluation. *PLoS One* 2017;**12**:e0184886.

43 Al-Janabi H, Van Exel J, Brouwer W et al. Measuring Health Spillovers for Economic Evaluation: A Case Study in Meningitis. *Health Econ* 2016;**25**:1529-1544.

44 Erickson LJ, De Wals P, McMahon J, Heim S. Complications of meningococcal disease in college students. *Clin Infect Dis* 2001;**33**:737-9.

45 Koomen I, Grobbee DE, Jennekens-Schinkel A, Roord JJ, van Furth AM. Parental perception of educational, behavioural and general health problems in school-age survivors of bacterial meningitis. *Acta Paediatr* 2003;**92**:177-85.

46 Oostenbrink R, HA AM, Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. *J Clin Epidemiol* 2002;**55**:791-9.

47 Al-Janabi H, Peters TJ, Brazier J et al. An investigation of the construct validity of the ICECAP-A capability measure. *Qual Life Res* 2013;**22**:1831-40.

48 Al-Janabi H, Flynn TN, Coast J. Estimation of a preference-based carer experience scale. *Med Decis Making* 2011;**31**:458-68.

49 EQ-5D-5L Health Questionnaire, English version for Australia. Netherlands: EuroQol Group EQ-5D, 2009.

50 Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* 2009;**41**:1149-1160.

51 Murray CJ, Lopez AD, Organization WH. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: summary. 1996.

52 Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 5.0), Canberra: Australian Government Department of Health and Ageing 2016, https://pbac.pbs.gov.au/ (Accessed 12th July 2018).

53 Collins J, Alona I, Tooher R, Marshall H. Increased awareness and health care provider endorsement is required to encourage pregnant women to be vaccinated. *Hum Vaccin Immunother* 2014;**10**:2922-9.

54 Pharmaceutical Benefits Advisory Committee. Multicomponent Meningococcal Group B Vaccine, 0.5mL, injection, prefilled syringe, Bexsero® - November 2013, Canberra, Australia: Pharmaceutical Benefits Scheme 2013, http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-11/meningococcal-vaccine (Accessed 12th July 2018).

55 -. Multicomponent Meningococcal Group B Vaccine, 0.5mL, injection, prefilled syringe, Bexsero® - July 2014, Canberra, Australia: Australian Government Department of Health 2014, http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2014-07/meningococcal-vaccine-psd-07-2014 (Accessed 12th July 2018).

56 -. Multicomponent Meningococcal Group B Vaccine (4CmenB); 0.5 mL suspension for injection pre-filled syringe; Bexsero® - July 2015, Canberra, Australia: Pharmaceutical Benefits Scheme 2015, http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2014-07/meningococcal-vaccine-psd-07-2014 (Accessed 12th July 2018).

Authors' contributions:

HM is the lead investigator on the AMEND study and designed the study protocol with BB, RB, PR, CB, MM, BW and HH. All the authors participated in the drafting and revision of the manuscript and approved the final version and agree to be accountable for the contents and integrity of this manuscript.

Funding

Funding for this study was provided by Pfizer. Pfizer was provided the opportunity to review a preliminary version of this manuscript for factual accuracy but the authors are solely responsible for final content and interpretation. The funder will not be involved in study processes, analysis or interpretation of the data. The authors received no financial support or other form of compensation related to the development of the manuscript.

Competing interests

HM is supported by a 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's and MM's institution receives funding for investigator-led studies from Industry (Pfizer, GSK). HM and MM receive no personal payments from Industry. CB is supported by a 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 has received research funding support from Sanofi-Pasteur for an unrelated study and has been an investigator on non-meningococcal vaccine studies sponsored by Industry (Sanofi-Pasteur). RB has received funding from Baxter, CSL/Seqirus, GSK, Merck, Novartis, Pfizer, Roche, Romark and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences or consultancy

work; all funding received is directed to research accounts at The Children's Hospital at Westmead.

Hossein Haji Ali Afzali is a member of the Australian Evaluation Sub-Committee (ESC) of the Medical Services Advisory Committee (MSAC).

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 25
	5b	Name and contact information for the trial sponsor	1, 25
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8. 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12, 13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 8, 9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	N/A
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13, 15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	No
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	No
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The AMEND Study Protocol: A case-control study to assess the long-term impact of invasive meningococcal disease in Australian adolescents and young adults

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032583.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Nov-2019
Complete List of Authors:	Marshall, Helen; University of Adelaide, Robinson Research Institute and Adelaide Medical School; Women's and Children's Health Network, Vaccinology and Immunology Research Trials Unit McMillan, Mark; The University of Adelaide, Robinson Research Institute and Adelaide Medical School; Women's and Children's Health Network, Vaccinology and Immunology Research Trials Unit Wang, Bing; The University of Adelaide, Robinson Research Institute and Adelaide Medical School; Women's and Children's Health Network, Vaccinology and Immunology Research Trials Unit Booy, Robert; The Children's Hospital at Westmead, The Discipline of Child and Adolescent Health; The Children's Hospital at Westmead, National Centre for Immunisation Research and Surveillance (NCIRS) Afzali , Hossein; Univeristy of Adelaide, School of Public Health Buttery, Jim; Royal Children's Hospital, Department of Paediatrics Blyth, Christopher C.; Perth Children's Hospital, Department of Infectious Diseases Richmond, Peter; University of Western Australia and Wesfarmers centre of Vaccines and Infectious Diseases, Telethon Kid's Institute, School of Medicine Shaw, David; SA Health, Infectious Diseases Service Gordon, David; Flinders Medical Centre, Microbiology and Infectious Diseases Barton, Belinda; The Children's Hospital at Westmead, Children's Hosptial Education Research Institute
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Public health, Infectious diseases, Health policy, Health economics
Keywords:	meningococcal disease, sequelae, neurocognitive, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, adolescents, young adults

The AMEND Study Protocol: A case-control study to assess the long-term impact of invasive meningococcal disease in Australian adolescents and young adults

Authors: Helen S Marshall [1,2], Mark McMillan [1,2] , Bing Wang [1,2], Robert Booy[3,4], Hossein Haji Ali Afzali[5], Jim Buttery[6], Christopher C Blyth[7], Peter Richmond[8], David Shaw[9], David L Gordon[10], Belinda Barton[11]

Corresponding Author: Helen Marshall, Women's and Children's Hospital, 72 King William Rd, North Adelaide, 5006, SA, Australia T: +61 8 8161 8115 Fax: +61 8 8161 7031
E: *helen.marshall@adelaide.edu.au*

Affiliations:

1. Vaccinology and Immunology Research Trials Unit, Women's and Children's Health Network, Adelaide, South Australia, Australia
2. Robinson Research Institute and Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia
3. The Discipline of Child and Adolescent Health, the Children's Hospital at Westmead Clinical School, The University of Sydney Medical School, Australia.
4. National Centre for Immunisation Research and Surveillance (NCIRS), The Children's Hospital at Westmead, NSW, Australia
5. School of Public Health, University of Adelaide, Adelaide, South Australia, Australia
6. Department of Paediatrics, Royal Children's Hospital, Victoria, Australia
7. Department of Infectious Diseases, Perth Children's Hospital, Western Australia
8. School of Medicine, University of Western Australia and Wesfarmers centre of Vaccines and Infectious Diseases, Telethon Kid's Institute, Perth, Western Australia
9. Infectious Diseases Service, Central Health Service, South Australia, Australia
10. Microbiology and Infectious Diseases, SA Pathology, Flinders Medical Centre, Bedford Park, South Australia, Australia
11. Children's Hospital Education Research Institute, The Children's Hospital at Westmead, Sydney, Australia

Keywords: meningococcal disease, sequelae, neurocognitive, health economics, immunisation programs, adolescents, young adults

Sponsor: The University of Adelaide

Funding: Pfizer

Word Count: 4803 (excluding title page, abstract, tables, strengths and limitations, acknowledgements, contributions and references). In response to reviewer feedback, we have provided more detail. This has taken us 803 words over the limit.

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 programs 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 post hospitalisation 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 odds ratio, or if any significant confounders are identified, adjusted analyses (ANCOVA or adjusted odds ratio) 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 study has been approved by the Women's and Children's Health Network Human Research Ethics Committee HREC/14/WCHN/024. Results will be disseminated via peer-reviewed publications, conference presentations, study participants, and meningococcal and meningitis foundations.

Trial registration

Clincialtrials.gov:NCT03798574

Strengths and limitations of this study

- Generation of new evidence to inform vaccination policy for protecting adolescents and young adults from 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 generalizability of the data to Australia and similar countries like New Zealand, Canada, United Kingdom and the United States.
- 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 provides 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 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 a 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.

Whilst meningococcal disease affects all age groups, the incidence of IMD peaks in the 0 to 4 year, and 15 to 25 year 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 to 25 years old 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] Results from a study of young adult males (18 to 24 years old at the time of IMD) conducted over 30 years ago indicated that 3 to 15 years post IMD, survivors reported

significantly more symptoms of possible sequelae compared to 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 old at time of IMD) who were followed up 18 to 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 to matched controls.[6] Adolescent survivors also reported significantly poorer physical and mental health (i.e. depression) as well as QoL when compared to 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 programs 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 (e.g. 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 programs 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 program which is provided for infants. Due to increasing incidence of

meningococcal W IMD cases in the UK a funded MenACWY vaccine program has been introduced.[21] In Australia a MenACWY program 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 programs provide 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 program, but detailed and contemporary data on the clinical benefit and long-term costs are not available, particularly for AYA.[23]

Findings from this study will assist in more robust data to inform policy as to whether meningococcal vaccines should be included in routine immunisation programs. 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 health care interventions and to inform public health policies such as funding priorities and immunisation programs.[25-27]

In summary, survivors of IMD experience a range of mild to severe sequelae that impact upon 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 i) assessing the impact of IMD on neurocognitive (academic achievement, executive functioning, memory), psychological and physical functioning; ii) estimating the lifetime costs associated with survival following IMD and iii) 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 multi-centre, 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 hospitalized 2 to 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 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 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 polymerase chain reaction (PCR), culture or cerebrospinal fluid (CSF) with *N. meningitidis* of any serogroup which will be verified by the site nurse or doctor.

- IMD cases must be aged 15 years to 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 to 10 years at the time of study assessments (retrospective).
- Controls will be aged 17 to 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 to 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 to 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 disclose their case/control status to the psychologist. On completion of all outcome measures participants will be provided with a $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 standardized test of intelligence.

QoL will be measured by the overall multi-attribute 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). Self-reported questionnaires assessing attention, executive functioning, behavior and psychological problems will also be completed by participants (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.

Table 1 Neurocognitive and psychological outcomes

Domain	Test	Age Range
Intelligence	Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV)[30]	16 to 90 years
Academic Achievement	Wechsler Individual Achievement Test - Second Edition (WIAT-II)[34] subtests: reading, spelling, maths reasoning, reading comprehension	4 years - adults
Executive Functioning	Delis–Kaplan Executive Function System (D-KEFS)[35] subtests: Trail Making Test, Color Word Interference Test, Verbal Fluency Test, Sorting Test	8 to 89 years
	Behavior Rating Inventory of Executive Function (BRIEF)[36] – parent	5-18 years
	BRIEF Adolescent self-report	11-18 years
	Behavior Rating Inventory of Executive Function - Adult self-report	≥ 18 years
Memory	Wide Range Assessment of Memory and Learning, Second Edition (WRAML2)[37] subtests: Verbal Learning and Design Memory	5-90 years
Psychiatric screening	Mini International Neuropsychiatric Interview (M.I.N.I. 6.0 kids)[38]	6 -17 years
	M.I.N.I 6.0 Adult[38]	≥ 18 years
	Depression Anxiety Stress Scales (DASS)[39]	>14 years
ADHD & problem	Conners Third Edition (Conners 3)[40] - Parent Full-length	6-18 years
	Conners 3[40] – Self-report Full length	8-18 years

Behavior	Conners Adult ADHD Rating Scales (CAARS)[41] Long Form: Self-Report	≥ 18 years
	CAARS Long Form: Observer	≥ 18 years

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 (ICF) tool to assess for the presence of body function/structure impairments, restrictions in physical activities and participation.[42] A pure tone audiometry will be conducted and hearing will be classified as no impairment (0) to profound (5).[43]

Quality of life (QoL) and carer experience

All participants will complete the EQ-5D-5L to measure their health status, which will be used to calculate quality adjusted life years (QALYS) 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. [32,33,44-48]

Table 2 Quality of life (QoL) and carer questionnaires

Domain	Test	Age Range	Completed by
Overall quality of Life	ICEpop CAPability measure for adults (ICECAP-A)[49]	≥ 18 years	Parent and other family members
Care-related quality of life	Carer Experience Scale (6 questions)[50]	≥ 18 years	Primary caregiver
Health-related quality of life	Health Utilities Index Mark 3 (HUI3)-15Q[31] Domains: vision, hearing, speech, cognition, pain, emotion, ambulation and dexterity.	≥ 15 years	Participant

Health status to calculate quality adjusted life years (QALYS) lost	EQ-5D-5L[51] (5 questions) Domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.	≥ 15 years	Participant

Socio-Economic Status (SES)

Socio-Economic Status of participants will be estimated using the Index of Relative Socio-Economic Advantage and Disadvantage, which ranks geographic areas in terms of their socio-economic advantage and disadvantage. [52] 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 demography (e.g. 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)[53] national program which subsidises the cost of a wide range of prescribed medicines for all Australians; and GP/specialist clinical records. IMD cases recruited prospectively will be asked to complete monthly diary cards for at least 12 months and up to 24 months depending upon 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

Semi-structured 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 semi-structured and consist of a series of questions (e.g. 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 to 10 years post diagnosis 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 stabilize 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 adverse event.

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,[6] 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 post intensive care discharge for IMD, HUI-3 overall scores were significantly lower by 0.11 when compared to 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 loss to follow-up) participants are required in each group.[54]

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 chi-squared or odds ratio (95% CI). However if any significant confounders (e.g. age, gender, SES) are identified then an adjusted analysis using ANCOVA and adjusted odds ratio (95% CI) will be conducted. All tests will be two-tailed with the Benjamini-Hochberg method applied to reduce the FDR by controlling for multiple hypotheses testing.[55] For continuous variables effect sizes (Cohen's *d*) will also be calculated.

For neurocognitive outcomes, level of impairment will also be classified by the number of standard deviations (SD) below the normative mean (mild: 1.0-1.9SD below, moderate: 2.0-2.9SD and severe: ≥3.0SD). 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 the World Health Organization Global Burden of Disease[56] 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 (e.g. 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. Odds ratio (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 to 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 assess the impact of any potential clustering on the outcomes and the conclusions of the study and to estimate correlation within clusters, for example using generalized 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 (e.g. visits to primary care physicians) and pharmaceuticals will be derived from Medicare including PBS.

Patient 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 (e.g. ambulance services) and co-payments (e.g. 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 (i.e. annual rates of 3.5% or 5%).[57] 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 (REF as the reviewer suggested). 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 top-down method, total health care costs would be disaggregated, and a relevant portion of the total costs would be allocated to a specific disease.[58] A decision analytic model (e.g. 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 (e.g. social, healthcare professionals) that they have received. Similar to methods used previously,[59] 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 re-read 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[60] 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 upon 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 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 (REDcap) database in a re-identifiable manner. The electronic database is username and password-protected and located on the server at the University of Adelaide. Except for 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 de-identified password protected dataset will be stored on the University of Adelaide server and deleted after 30 years.

Re-identifiable data is 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 which 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:

The study has been approved by the Women's and Children's Health Network Human Research Ethics Committee. Governance and ethics approval has also been obtained at all other affiliated sites. 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 (e.g. 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.

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. Results may also be reported on websites (e.g. 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 standardized 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 socioeconomic status. 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 United Kingdom Joint Committee on Vaccination and Immunisation initially concluded that an infant MenB vaccine program 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 program 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.[57,61-63] 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 programs.

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. 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.

REFERENCES

1. Hart CA, Thomson AP. Meningococcal disease and its management in children. *Bmj.* 2006;333(7570):685-690.

2. Chang Q, Tzeng YL, Stephens DS. Meningococcal disease: changes in epidemiology and prevention. *Clin Epidemiol.* 2012;4:237-245.

3. Jafri RZ, Ali A, Messonnier NE, et al. Global epidemiology of invasive meningococcal disease. *Popul Health Metr.* 2013;11(1):17.

4. Baker CJ. Prevention of meningococcal infection in the United States: current recommendations and future considerations. *Journal of Adolescent Health.* 2016;59(2):S29-S37.

5. 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):317-328.

6. Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. *Pediatrics.* 2009;123(3):e502-509.

7. 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 neurology.* 2012;11(9):774-783.

8. Lahra M, Enriquez R. Australian Meningococcal Surveillance Programme annual report, 2014. 2016; http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-pubs-annlrpt-menganrep.htm. Accessed 16th August, 2016.

9. 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.

10. Pelton SI. The Global Evolution of Meningococcal Epidemiology Following the Introduction of Meningococcal Vaccines. *J Adolesc Health.* 2016;59(2 Suppl):S3-S11.

11. Patton GC, Sawyer SM, Santelli JS, et al. Our future: a Lancet commission on adolescent health and wellbeing. *Lancet.* 2016;387(10036):2423-2478.

12. Keshavan MS, Giedd J, Lau JY, Lewis DA, Paus T. Changes in the adolescent brain and the pathophysiology of psychotic disorders. *Lancet Psychiatry.* 2014;1(7):549-558.

13. Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev.* 2000;24(4):417-463.

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

15. Wang B, Santoreneos R, Afzali H, Giles L, Marshall H. Costs of Invasive Meningococcal Disease: A Global Systematic Review. *Pharmacoeconomics.* 2018.

16. Borrow R, Alarcon P, Carlos J, et al. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. *Expert Rev Vaccines.* 2017;16(4):313-328.

17. Jit M, Hutubessy R. Methodological Challenges to Economic Evaluations of Vaccines: Is a Common Approach Still Possible? *Appl Health Econ Health Policy.* 2016;14(3):245-252.

18. Joint Committee on Vaccination and Immunisation (JCVI). JCVI interim position statement on use of Bexsero® meningococcal B vaccine in the UK 2013 Vol 2018. UK: Department of Health and Social Care; 2013.

19. 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):280-288.

20. European Centre for Disease Prevention and Control. Expert opinion on the introduction of the meningococcal B (4CMenB) vaccine in the EU/EEA. Stockholm: ECDC; 2017.

21. Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. Enter B and W: two new meningococcal vaccine programmes launched. *Arch Dis Child.* 2016;101(1):91-95.

22. Australian Technical Advisory Group on Immunisation. National Immunisation Program Schedule. Vol 2019. 10th ed. Canberra: Australian Government Department of Health; 2018.

23. Pharmaceutical Benefits Advisory Committee. Meningococcal polysaccharide conjugate vaccine serogroups A, C, W-135 and Y(adolescents): Pre-filled syringe, 0.5mL; Nimenrix® Pharmaceutical Benefits Scheme. Canberra: Department of Health, Australian Government; 2018.

24. Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. *Pharmacoeconomics.* 2011;29(8):653-671.

25. Byford S, Torgerson DJ, Raftery J. Economic note: cost of illness studies. *Bmj.* 2000;320(7245):1335.

26. Durand-Zaleski I. Why cost-of-illness studies are important and inform policy. *Vasc Med.* 2008;13(3):251-253.

27. Chisholm D, Saxena S, Van Ommeren M. Dollars, DALYs and decisions: economic aspects of the mental health system. Geneva: World Health Organization; 2006.

28. International statistical classification of diseases and related health problems 10th ed. Geneva: World Health Organisation; 2018.

29. The SAGE Encyclopedia of Social Science Research Methods. Thousand Oaks, California: Sage Publications, Inc. ; 2004.

30. Wechsler D. *Wechsler Adult Intelligence Scale-3rd Edition (WAIS-IV) Australian and New Zealand adaptation.* Sydney, NSW: Pearson; 2008.

31. Furlong WJ, Feeny DH, Torrance GW. *Health utilities index® mark 2 and mark 3 (hui2/3) 15-item questionnaire for Self-administered, self-assessed "four week" health status assessment.* Dundas ON Canada: Health Utilities Inc; 2016.

32. Kennedy ITR, van Hoek AJ, Ribeiro S, et al. Short-term changes in the health state of children with group B meningococcal disease: A prospective, national cohort study. *PLoS One.* 2017;12(5):e0177082.

33. Buysse CM, Raat H, Hazelzet JA, et al. Long-term health status in childhood survivors of meningococcal septic shock. *Arch Pediatr Adolesc Med.* 2008;162(11):1036-1041.

34. Wechsler D. *Wechsler Individual Achievement Test- Second Edition (WIAT-II).* London, UK: Psychological Corporation.; 2005.

35. Delis D, C Kaplan E, Kramer JH. *Delis-Kaplan Executive Function System.* San Antonio, TX: The Psychological Corporation; 2001.

36. Gioia G, Isquith P, Guy S, Kenworthy L. *Behavior Rating Inventory of Executive Function (BRIEF).* Lutz, Florida: Psychological Assessment Resources; 2000.

37. Sheslow D, Adams W. *Wide Range Assessment of Memory and Learning, Second Edition (WRAML2).* Bloomington: Pearson; 2003.

38. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* 1998;59 Suppl 20:22-33;quiz 34-57.

39. Psychology Foundation of Australia. Depression Anxiety Stress Scales (DASS). UNSW: Psychology Department, UNSW; 2014.

40. Conners K ED, Sparrow E,. *Conners 3rd edition (Conners) Manual.* Canada: Multi-Health Systems Inc; 2009.

41. Conners K ED, Sparrow E, . *Conners' Adult ADHD Rating Scales.* Canada: Multi-Health Systems Inc; 2002.

42. Kostanjsek N. Use of The International Classification of Functioning, Disability and Health (ICF) as a conceptual framework and common language for disability statistics and health information systems. *BMC Public Health.* 2011;11(Suppl 4):S3-S3.

43. Mathers C, Smith A, Concha M. Global burden of hearing loss in the year 2000. *Global burden of Disease.* 2000;18(4):1-30.

44. Al-Janabi H, Manca A, Coast J. Predicting carer health effects for use in economic evaluation. *PLoS One.* 2017;12(9):e0184886.

45. Al-Janabi H, Van Exel J, Brouwer W, et al. Measuring Health Spillovers for Economic Evaluation: A Case Study in Meningitis. *Health Econ.* 2016;25(12):1529-1544.

46. Erickson LJ, De Wals P, McMahon J, Heim S. Complications of meningococcal disease in college students. *Clin Infect Dis.* 2001;33(5):737-739.

47. Koomen I, Grobbee DE, Jennekens-Schinkel A, Roord JJ, van Furth AM. Parental perception of educational, behavioural and general health problems in school-age survivors of bacterial meningitis. *Acta Paediatr.* 2003;92(2):177-185.

48. Oostenbrink R, HA AM, Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. *J Clin Epidemiol.* 2002;55(8):791-799.

49. Al-Janabi H, Peters TJ, Brazier J, et al. An investigation of the construct validity of the ICECAP-A capability measure. *Qual Life Res.* 2013;22(7):1831-1840.

50. Al-Janabi H, Flynn TN, Coast J. Estimation of a preference-based carer experience scale. *Med Decis Making.* 2011;31(3):458-468.

51. *EQ-5D-5L Health Questionnaire, English version for Australia.* Netherlands: EuroQol Group EQ-5D; 2009.

52. Statistical Local Area, Table 2: Socio-Economic Indexes for Areas (SEIFA), data cube: Excel spreadsheet, cat. no. 2033.0.55.001. 2011; http://www.abs.gov.au/ausstats/abs@.nsf/DetailsPage/2033.0.55.0012011?OpenDocument . Accessed 21 September 2017.

53. Pharmaceutical Benefits Scheme www.pbs.gov.au. Accessed 10 November 2019.

54. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods.* 2009;41(4):1149-1160.

55. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (Methodological).* 1995;57(1):289-300.

56. Murray CJ, Lopez AD, Organization WH. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: summary. 1996.

57. Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (version 5.0). Vol 2018. Canberra: Australian Government Department of Health and Ageing; 2016.

58. Frick KD. Micro-costing quantity data collection methods. *Medical care.* 2009;47(7 Suppl 1):S76.

59. Collins J, Alona I, Tooher R, Marshall H. Increased awareness and health care provider endorsement is required to encourage pregnant women to be vaccinated. *Hum Vaccin Immunother.* 2014;10(10):2922-2929.

60. Tariq S, Woodman J. Using mixed methods in health research. *JRSM short reports.* 2013;4(6):2042533313479197.

61. Pharmaceutical Benefits Advisory Committee. Multicomponent Meningococcal Group B Vaccine, 0.5mL, injection, prefilled syringe, Bexsero® - November 2013. Vol 2018. Canberra, Australia: Pharmaceutical Benefits Scheme; 2013.

62. Pharmaceutical Benefits Advisory Committee. Multicomponent Meningococcal Group B Vaccine, 0.5mL, injection, prefilled syringe, Bexsero® - July 2014. Vol 2018. Canberra, Australia: Australian Government Department of Health; 2014.

63. Pharmaceutical Benefits Advisory Committee. Multicomponent Meningococcal Group B Vaccine (4CmenB); 0.5 mL suspension for injection pre-filled syringe; Bexsero® - July 2015. Vol 2018. Canberra, Australia: Pharmaceutical Benefits Scheme; 2015.

Authors' contributions:

HM is the lead investigator on the AMEND study and designed the study protocol with BB, RB, PR, CB, MM, BW, JB, DS, DG, and HA. All the authors participated in the drafting and revision of the manuscript and approved the final version and agree to be accountable for the contents and integrity of this manuscript.

Funding

Funding for this study was provided by Pfizer. Pfizer was provided the opportunity to review a preliminary version of this manuscript for factual accuracy but the authors are solely responsible for final content and interpretation. The funder will not be involved in study processes, analysis or interpretation of the data. The authors received no financial support or other form of compensation related to the development of the manuscript.

Competing interests

HM is supported by a 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's and MM's institution receives funding for investigator-led studies from Industry (Pfizer, GSK). HM and MM receive no personal payments from Industry. CB is supported by a 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 has received research funding support from Sanofi-Pasteur for an unrelated study and has been an investigator on non-meningococcal vaccine studies sponsored by Industry (Sanofi-Pasteur). RB has received funding from Baxter, CSL/Seqirus, GSK, Merck, Novartis, Pfizer, Roche, Romark and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences or consultancy

work; all funding received is directed to research accounts at The Children's Hospital at Westmead. Hossein Haji Ali Afzali is a member of the Australian Evaluation Sub-Committee (ESC) of the Medical Services Advisory Committee (MSAC).

Figure 1: AMEND Study recruitment flow chart

[a] Invasive Meningococcal Disease

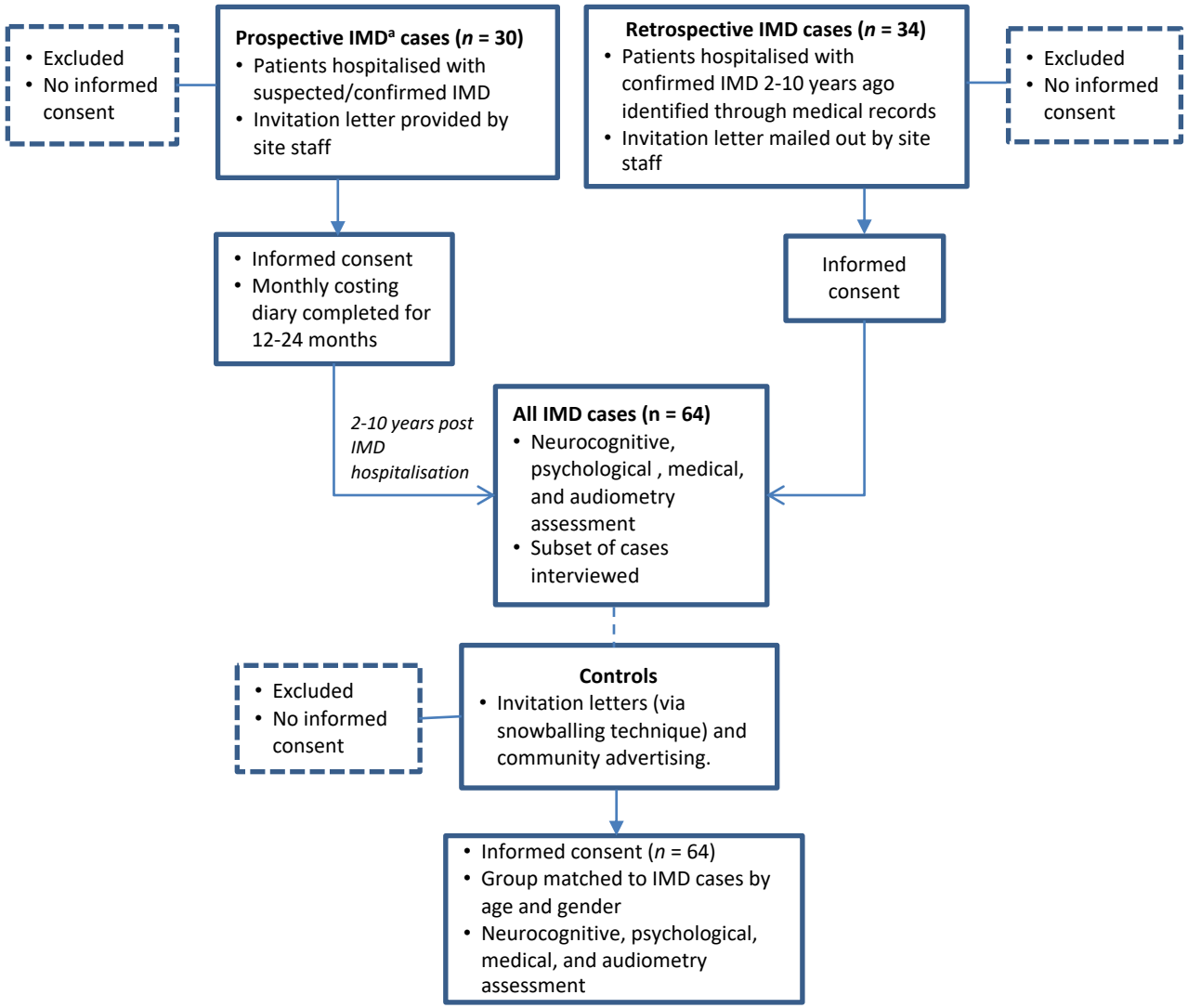

Figure 1: AMEND Study recruitment flow chart

[a] Invasive Meningococcal Disease

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 27
	5b	Name and contact information for the trial sponsor	1, 27
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7, 8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13, 14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17, 18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	N/A
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18,19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, 7, 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18, 19
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	No
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	No
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.