A Report on the Feasibility Study of the Proposed NT Pneumococcal Vaccine Trial

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Table of Contents

Acknowledgments ......................................................................................................... iv
Feasibility Study Team .................................................................................................. v
Glossary ....................................................................................................................... vi
Preface ......................................................................................................................... ix
Section 1
  Summary .................................................................................................................... 1
Section 2
  Overview & Results of the Feasibility Study ............................................................... 3
Section 3
  Scientific Design ....................................................................................................... 11
Section 4
  Logistics ..................................................................................................................... 17
Section 5
  Consultation ............................................................................................................. 55
Section 6
  Informed Consent .................................................................................................... 73
References .................................................................................................................. 79
Appendices ..................................................................................................................... 83
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The feasibility study team gratefully acknowledges and thanks you all.
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<th>FULL TITLE</th>
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<td>Australian Childhood Immunisation Register</td>
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<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AMA</td>
<td>Australian Medical Association</td>
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<tr>
<td>AMS</td>
<td>Aboriginal Medical Service</td>
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<tr>
<td>AMSANT</td>
<td>Aboriginal Medical Services Alliance of the Northern Territory</td>
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<tr>
<td>ASH</td>
<td>Alice Springs Hospital</td>
</tr>
<tr>
<td>ARDS</td>
<td>Aboriginal Resource Development Services</td>
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<tr>
<td>AUD</td>
<td>Australian Dollar</td>
</tr>
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<td>BIM</td>
<td>Business Information Management Unit</td>
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<td>CA</td>
<td>Central Australia</td>
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<tr>
<td>CAAC</td>
<td>Central Australian Aboriginal Congress</td>
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<td>CABAHWA</td>
<td>Central Australian &amp; Barkly Aboriginal Health Worker Association</td>
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<td>CARHTU</td>
<td>Central Australian Rural Health Unit</td>
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<td>CARPA</td>
<td>Central Australian Rural Practitioners Association</td>
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<tr>
<td>CBD</td>
<td>Central Business District</td>
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<tr>
<td>CCIS</td>
<td>Community Care Information System</td>
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<tr>
<td>CHC</td>
<td>Community Health Centre</td>
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<tr>
<td>CDC</td>
<td>Centre for Disease Control</td>
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<td>CINCRM</td>
<td>Centre for Indigenous Natural &amp; Cultural Resource Management (NTU)</td>
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<td>CLC</td>
<td>Central Land Council</td>
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<td>CRANA</td>
<td>Council of Remote Area Nurses Australia</td>
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<td>CRCATH</td>
<td>Cooperative Research Centre for Aboriginal &amp; Tropical Health</td>
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<td>CRH</td>
<td>Centre for Remote Health</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<tr>
<td>CXR</td>
<td>Chest x-ray</td>
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<tr>
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<td>Darwin Private Hospital</td>
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<tr>
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<td>Darwin Community Legal Service</td>
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<tr>
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<tr>
<td>FATSIS</td>
<td>Faculty of Aboriginal &amp; Torres Strait Islander Studies</td>
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<tr>
<td>GDH</td>
<td>Gove District Hospital</td>
</tr>
<tr>
<td>GP</td>
<td>General Practice</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline (formed by merger of Glaxo Wellcome and SmithKline Beecham in Jan 2001)</td>
</tr>
<tr>
<td>HIC</td>
<td>Health Insurance Commission</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
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</tr>
<tr>
<td>ICD9</td>
<td>International Classification of Disease - 9</td>
</tr>
<tr>
<td>IPD</td>
<td>Invasive Pneumococcal Disease</td>
</tr>
<tr>
<td>KDH</td>
<td>Katherine District Hospital</td>
</tr>
<tr>
<td>MCHN</td>
<td>Maternal and Child Health Nurse</td>
</tr>
<tr>
<td>MO</td>
<td>Medical Officer</td>
</tr>
<tr>
<td>NAALAS</td>
<td>Northern Australian Aboriginal Legal Aid Service</td>
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<td>National Aboriginal Community Controlled Health Organisations</td>
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<tr>
<td>NLC</td>
<td>Northern Land Council</td>
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<tr>
<td>NSAE</td>
<td>Non-Serious Adverse Events</td>
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<tr>
<td>NT</td>
<td>Northern Territory</td>
</tr>
<tr>
<td>NTCIR</td>
<td>Northern Territory Childhood Immunisation Register</td>
</tr>
<tr>
<td>NTHi</td>
<td>Non-typeable <em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>NTU</td>
<td>Northern Territory University</td>
</tr>
<tr>
<td>OPD</td>
<td>Out Patients’ Department</td>
</tr>
<tr>
<td>PHSU</td>
<td>Public Health Strategy Unit (THS)</td>
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<tr>
<td>QHSS</td>
<td>Queensland Health Scientific Services</td>
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<tr>
<td>QML</td>
<td>Queensland Medical Laboratories</td>
</tr>
<tr>
<td>RAET</td>
<td>Remote Area Education Team</td>
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<tr>
<td>RDH</td>
<td>Royal Darwin Hospital</td>
</tr>
<tr>
<td>SA</td>
<td>South Australia</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SB</td>
<td>SmithKline Beecham Biologicals</td>
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<tr>
<td>SDS</td>
<td>Staff Development Services (THS)</td>
</tr>
<tr>
<td>TCH</td>
<td>Tennant Creek Hospital</td>
</tr>
<tr>
<td>TCK</td>
<td>Tennant Creek</td>
</tr>
<tr>
<td>THS</td>
<td>Territory Health Services</td>
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Preface

This report describes the findings of a Feasibility Study for a proposed pneumococcal conjugate vaccine trial in the Northern Territory. The study was conducted between February and September 2000. At its conclusion, the Cooperative Research Centre for Aboriginal & Tropical Health (CRCATH) agreed to support a trial proceeding in three regions in the Northern Territory. An agreement was reached with the sponsor, SmithKline Beecham Biologicals (SB), for funding of a preparatory phase.

The preparatory phase commenced in October 2000 with Dr Jonathan Carapetis as the Principal Investigator. A start date for the trial was set for 31 January 2001. At the end of November the following milestones were achieved:

- the scientific protocol was finalised and approved by SB;
- a project budget was ready for submission to SB;
- preliminary clearance for Phase I of the study had been granted by the Top End Ethics Committee and applications were submitted to the Central Australian Ethics Committee and the Tiwi Health Board;
- consultation with the relevant communities and organisations had commenced;
- informed consent materials were finalised and readied for production;
- the development of study infrastructure had commenced including recruitment of staff, and identification of equipment and resources;
- data management processes had commenced;
- plans for adverse event monitoring and endpoint measurements were well advanced; and
- staff training packages had been developed.

In mid-November 2000, the investigators received indications that an alternative vaccine produced by Wyeth-Lederle (Prevenar™) would be registered for use in Australia in early December, and introduction into Aboriginal communities at some time during the first half of 2001 could be anticipated. Introduction of Prevenar™ might well occur during the planned catch-up phase of the NT study. It was thought this would lead to several problems including:

- a reduced confidence in the ability to achieve primary endpoints in the time required;
- a potentially significant drop in recruitment rates as parents would have to choose between a licensed and an unlicensed vaccine;
- difficulty in attributing any observed change in disease incidence if both vaccines were in use; and
- ethical difficulties in conducting a trial of an unlicensed product for which no efficacy data are available when a licensed alternative was available.

Based on the available information, the study’s International Advisory Board (IAB) was convened for advice on whether to proceed with the trial.

It was agreed that there were major risks to the trial being successfully completed and that the benefits of the trial to communities were substantially less given a licensed vaccine would be available earlier that previously anticipated. The CRCATH and the Principal Investigator therefore agreed that it would be unethical to proceed. SB concurred with the decision and the study was cancelled on November 15.
Despite the cancellation there are several positive outcomes of the process, not the least being the collaborative relationships that have been developed between the CRCATH, researchers and SB in the Northern Territory, as well as those that have been strengthened with health services and communities. Importantly, new skills and knowledge have been developed for future health research and there is now an increased awareness of the public health importance of pneumococcal disease in the NT.
1. Summary

Pneumococcal infections are a major health problem for children in the Northern Territory (NT). The pneumococcal bacterium (*Streptococcus pneumoniae*) causes serious illnesses including meningitis, pneumonia and otitis media. Invasive Pneumococcal Disease (IPD) refers to internal infections that are confirmed as due to pneumococcus by isolation of the organism from usually sterile body sites, most commonly blood or CSF. The incidence of IPD in NT children aged under two years is higher than in other Australian children, particularly in Aboriginal children and in Central Australia.\(^1\)\(^2\) IPD is only a small part of the problem caused by pneumococcus – many more cases of pneumonia are treated without being microbiologically confirmed, and otitis media damages the hearing of a quarter or more of Aboriginal children.\(^3\)\(^4\)

The existing pneumococcal vaccine (Pneumovax™) is of limited benefit in children under age two years. Pharmaceutical companies have recently developed a new type of vaccine, called a conjugate vaccine, which does work in infants. This is the same type of vaccine as the Hib vaccine which has almost wiped out serious Hib infections in children since being introduced as a routine childhood vaccine in 1993.

In mid-1999 the pharmaceutical company SmithKline Beecham Biologicals (SB) proposed that the Cooperative Research Centre for Aboriginal and Tropical Health conduct an effectiveness trial of their new conjugate pneumococcal vaccine in the NT. The proposal was to offer the new vaccine to all children up to age two at the start of the trial and all children born for the following three years, approximately 18,000 children.

In November 1999 the CRCATH Board requested that SB fund a feasibility study of this proposal. In December 1999, SB agreed to fund the feasibility study, which commenced on 1 March 2000.

The study focused on three main issues:

1. the scientific design and logistical aspects of conducting the trial, including estimated cost and potential impact on existing primary health care services (including the routine childhood immunisation program);
2. whether there was a sufficient level of support for the proposed trial in health services and the community generally; and
3. whether an adequate informed consent process could be conducted for a trial of this scale involving such a diverse range of Aboriginal and non-Aboriginal people.

The feasibility study found that there is general (although not unanimous) support for the trial from health professionals, health service management, key policy officers and senior management of Territory Health Services (THS), and some community organisations such as the Boards of community-controlled Aboriginal health services.

However, important practical issues were raised by health care providers including additional workload on primary health care staff and the potential confusion of parents about the routine childhood vaccination schedule. These issues were taken into account in modifying the study design and developing implementation plans.

Several informed consent processes and information materials from other research projects, clinical procedures and health promotion activities were assessed. A model for information materials was developed for the trial based on an award-winning health education project about rheumatic heart disease.

Full development and testing of a community consultation and informed consent process was not possible during the feasibility study. This work remained to be completed during the preparatory phase of the trial.

Information obtained from consultation with primary health care providers and assessment of logistical issues indicated early during the feasibility study that the trial as originally proposed (entire NT for three years, closely integrated into the routine vaccination system) was not feasible. Options to reduce the scope of the trial were considered, including a trial restricted to Central Australia and the Tiwi Islands. There was a high level of support for this option in Central Australia, and there did not appear to be major logistical obstacles to successfully completing such a trial.
However, in June 2000 it became apparent that an alternative conjugate pneumococcal vaccine, Prevenar™ manufactured by Wyeth Lederle, was very likely to be introduced as a routine childhood vaccine for Aboriginal children, and possibly for all NT children, in the second half of 2001.

There was felt to be good reason to proceed with a trial of the SB vaccine despite the availability of Prevenar™ – the SB vaccine contains four more serotypes of pneumococcus than Prevenar™, and a carrier protein that may offer protection against Haemophilus infections. However, the likely introduction of Prevenar™ posed serious practical difficulties for the trial including a more complex informed consent process, a reduction in the number of children recruited to the trial and more complex interaction with primary health care services responsible for routine childhood immunisation.

These problems did not rule out conducting the trial in Central Australia, but they considerably increased the risk that the trial could not be successfully completed. After consultation with senior staff of THS responsible for immunisation policy and with health service organisations in Central Australia, the feasibility study team determined that the risk of the trial not being successfully completed was too high to proceed, despite the high level of support to conduct the trial from Central Australian health services.

The feasibility study then investigated the option to reduce the scope of the trial by focusing on otitis media and pneumonia as the primary outcome measures instead of IPD. This required fewer children to be involved because otitis media and pneumonia are far more common conditions than IPD and so the effect of the vaccine on these conditions can be seen in a smaller number of children. This trial could be conducted in three areas instead of all of Central Australia, and would need to recruit children for only one year instead of two which it was hoped would substantially reduce or eliminate the period of overlap with Prevenar™.

The feasibility study recommended to the CRCATH Board in August 2000 that the larger scale trial with IPD as the primary outcome should not proceed, but that a smaller scale trial focusing on pneumonia and otitis media, should be fully developed and proposed to SB. The Board accepted this recommendation. This design was developed further, including review by the feasibility study’s International Advisory Committee, and a protocol synopsis and detailed cost estimate were submitted to SB in mid-September.

On 6 October written advice was received from the Biologicals Medical Director of SB Australia that the synopsis and cost estimate had been approved by the company, and the project would be funded to commence preparatory work immediately.
2. Feasibility Study Overview

In late 1999 the pharmaceutical company, SmithKline Beecham Biologicals (SB) proposed to the Board of the Cooperative Research Centre for Aboriginal and Tropical Health (CRCATH) that a clinical trial of a new childhood vaccine against pneumococcal infections be conducted in the Northern Territory (NT). This proposal came after considerable discussion with communicable disease experts and representatives of health and research organisations in the NT and elsewhere.

Pneumococcal disease occurs much more frequently in the NT, particularly in Aboriginal children, than elsewhere in Australia and most of the world. The CRCATH Board was interested in this proposal, but concerned that the project was of a much larger scale than any previously conducted in the NT and that there may not be sufficient support for such a trial from health services and the general public.

At its meeting in November 1999 the Board commissioned a feasibility study of this proposal, which was funded by SB. The NT Government approved the involvement of Territory Health Services (THS) in the feasibility study in late February, and the study commenced in March 2000, to be completed by 5 September 2000.

The three main issues to be addressed by the feasibility study were:

1. the scientific design and logistical aspects of conducting the trial as proposed, including estimated cost and potential impact on existing primary health care services (including the routine childhood immunisation program);
2. whether there was a sufficient level of support for the proposed trial in health services and the community generally; and
3. whether an adequate informed consent process could be conducted for a trial of this scale involving such a diverse range of Aboriginal and non-Aboriginal people.

2.1. Pneumococcal Disease

The bacterium *Streptococcus pneumoniae* (commonly called pneumococcus) causes serious illness in children, including meningitis, pneumonia and middle ear infections (otitis media).

Invasive Pneumococcal Disease (IPD) refers to serious infections of the brain (meningitis), lungs (pneumonia) and blood (bacteraemia) and other internal parts of the body caused by pneumococcus, which are confirmed by isolation of pneumococcus from normally sterile sites. Pneumococcus causes these infections in people of any age, but children under the age of two years are the most commonly affected. Pneumococcus is also known to be the most important cause of otitis media, the ear disease that is very common in Aboriginal children. Chronic otitis media causes considerable hearing loss in many children, and seriously affects their education.

Between 1994 and 1998 inclusive there were an average of 27 confirmed cases of IPD in the NT in children aged under two, almost all seriously ill requiring hospital treatment, with an average of one death per year. The incidence of IPD in children aged under two in the Northern Territory is higher than in other parts of Australia, for both Aboriginal and non-Aboriginal children.

Compared to other Australian children, the incidence of IPD in Aboriginal children is approximately three times higher in the Top End and 15 times higher in Central Australia. In Central Australia the incidence in non-Aboriginal children is also higher, about double that of other Australian children, while for non-Aboriginal children in the Top End the incidence is similar to other Australian children. It is not known why the disease is so much more common in Central Australia.
Table 1: Invasive Pneumococcal Disease, children under two years, NT 1994-1998*

<table>
<thead>
<tr>
<th></th>
<th>Aboriginal</th>
<th>non-Aboriginal</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Number of cases - Central Australia</td>
<td>80</td>
<td>9</td>
<td>89</td>
</tr>
<tr>
<td>Number of cases - Top End</td>
<td>31</td>
<td>15</td>
<td>46</td>
</tr>
<tr>
<td>Total NT cases</td>
<td>111</td>
<td>24</td>
<td>135</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Ave Length of Hospital Stay (days)</td>
<td>14.5</td>
<td>4.8</td>
<td></td>
</tr>
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*Krause 2000

Table 2: Invasive Pneumococcal Disease incidence, children under two years

<table>
<thead>
<tr>
<th>Incident rate (per 100 000)</th>
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<tbody>
<tr>
<td>Sydney*</td>
</tr>
<tr>
<td>Central Australia**</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Top End**</td>
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*1997-99, McIntyre 2000
** 1994-98, Krause 2000

Invasive pneumococcal disease is only the ‘tip of the iceberg’ of serious pneumococcal illness in young children. Acute Lower Respiratory Infections (ALRI), which include pneumonia, are frequent and serious illnesses in Aboriginal children.7;8 Pneumococcus is a common cause of ALRI, and causes a particularly serious form of pneumonia. The cause of ALRI is difficult to determine, and in most cases ALRI is treated without, or before, any diagnostic tests being done. Even if they are done, blood cultures are only positive in a small proportion of cases of pneumococcal pneumonia.

While rates have been declining over the past 15 years, the death rate from infectious respiratory diseases remains up to 15 times higher in NT Aboriginal people than Australians overall (THS, unpublished data). Between 1993 – 1997, 18 per cent of Aboriginal children and 5 per cent of non-Aboriginal children admitted to hospital were treated for ALRI, as either the main condition or a secondary condition treated (THS, unpublished data).

Otitis media is very common and begins within the first few months of life in NT Aboriginal infants. Several NT studies have shown that up to one-third of Aboriginal children have ear drum perforation by six months of age and that up to two-thirds of these infants have perforation by the age of 12 months.3;4;7;9;10 The World Health Organisation recommends that if more than four percent of children have an eardrum perforation this should be considered a massive public health problem requiring urgent attention.11 Pneumococcus is believed to be one of the main causes of otitis media, although other bacteria (including H. influenzae), and possibly some viruses, are also important causes. Treatment of otitis media is currently very difficult, with no simple, effective antibiotic treatment available.
2.2 The SmithKline Beecham Conjugate Pneumococcal Vaccine

The existing vaccine against pneumococcal infections (Pneumovax™) works in older children and adults, but has limited benefit in children under the age of two years, those at highest risk. Several pharmaceutical companies have recently developed a new type of pneumococcal vaccine (called a ‘conjugate’ vaccine) that does stimulate an immune response in infants. The technology used to produce these vaccines is similar to that used for the *Haemophilus influenzae* type B (Hib) vaccine, which has been so successful in reducing serious bacterial infections, including meningitis, in Aboriginal and non-Aboriginal children. These vaccines are designed to prevent meningitis and pneumonia. They may also have some effect in preventing otitis media due to pneumococcus.

There are over 90 different types (serotypes) of pneumococcus, but most serious infections are caused by only a small number of these. The conjugated vaccine developed by SB contains the eleven most common types of pneumococcus worldwide. These eleven serotypes caused 67 per cent of the 135 cases of invasive pneumococcal disease in NT children aged under two years between 1994 and 1998.1 The SB vaccine also contains a carrier protein derived from the *H. influenzae* bacteria.13 This protein, known as protein D, is highly conserved across different *H. influenzae* bacteria. It has been shown in a variety of animal models, to accelerate clearance of ear and lung infections due to non-typeable *H. influenzae*. Like pneumococcus, non-type B *H. influenzae* also causes respiratory and ear infections in children. The SB vaccine may have some effect against *H. influenzae* in humans as well as against the eleven serotypes of *S. pneumoniae*.14 Conjugate pneumococcal vaccines produced by other manufacturers do not contain this carrier protein.

It is likely that the SB vaccine will reduce the occurrence of otitis media in Aboriginal children to some extent, but at this stage this is only a possibility that needs to be investigated further. Otitis media caused by bacteria other than pneumococcus or haemophillus will not be affected by this vaccine. A realistic expectation is that the new vaccine may reduce chronic otitis media by between 10 and 30 per cent. A greater reduction is possible, although this is difficult to predict.

The SB pneumococcal vaccine is not yet licensed for general use. Phase I clinical trials have been completed. Phase II clinical trials are almost completed. All of these trials to date indicate that the vaccine is safe and elicits an immune response against the pneumococcal serotypes included in the vaccine, both in children and in adults. The Australian Therapeutic Goods Administration (TGA) approved the conduct of clinical trials using this vaccine (under the CTX scheme) in mid-October 2000.

2.3 Proposed clinical trial in the Northern Territory

The original proposal for a clinical trial of the SB pneumococcal vaccine in the NT was to offer the vaccine to all children aged under two years, and all newborn children for the following three years. The trial was to be conducted largely through the existing childhood vaccination system administered by primary health care services (Community Health Centres, Aboriginal Medical Services and General Practitioners). The primary outcome measure was to be IPD.

There are approximately 3,600 children born each year in the NT. This proposal would have included all children born over a five year period (those born two years before the project started and for the three years of the project). Approximately 18,000 children and their parents would have been approached about participating in the trial, and if only 70 per cent actually enrolled there would have been over 12,000 children recruited.

This study was first proposed to the administration of the CRCATH in mid-1999. After several meetings of senior policy staff, health professionals and researchers, including representatives of Aboriginal Medical Services (AMSs), in Darwin in the second half of 1999, the proposal was considered by the CRCATH Board in November 1999. The Board was interested, but concerned that such a large-scale research project, of an unlicensed vaccine, may not be possible in the NT, or may not have sufficient community or health sector support, to be successful. The Board requested that SB fund a feasibility study.
A Feasibility Study Proposal, including cost estimate, was developed for the CRCATH by Dr Christine Connors, Senior District Medical Officer, Darwin Rural District, THS (see Appendix A). This proposal was accepted and funded by SB in mid-December 1999. Dr John Condon commenced as Principal Investigator for the feasibility study in January 2000, but commencement was delayed while NT Government approval was sought for THS to be involved in the project. The study commenced on 1 March 2000 after this approval was obtained, with a completion date set at 5 September 2000.

The study investigated three main issues:

1. the scientific design and logistical aspects of conducting the trial as proposed, including estimated cost and potential impact on existing primary health care services (including the routine childhood immunisation program);
2. whether there was a sufficient level of support for the proposed trial in health services and the community generally; and
3. whether an adequate informed consent process could be conducted for a trial of this scale involving such a diverse range of Aboriginal and non-Aboriginal people.

Detailed reports on each area of investigation are included in Sections Three to Six of this report.

2.4 Potential benefits and risks of conducting the trial

The feasibility study identified the following potential benefits and risks from conducting the proposed trial:

*Direct benefits to NT children*

- early introduction of a conjugate pneumococcal vaccine in children aged under two
- the SB vaccine may prevent approximately eight percent more cases of invasive pneumococcal disease than the alternative vaccine Prevenar™ (the SB vaccine covers eleven serotypes while Prevenar™ covers only seven)
- the SB vaccine may prevent some *Haemophilus influenzae* infections not prevented by the Hib vaccine because it contains a *H. influenzae* protein which may offer some protection against non-typable *Haemophilus* infections

*Indirect benefits*

- the increased resources for vaccination may improve coverage of the routine vaccination schedule
- increased public awareness in the NT about pneumococcal infections, ear disease and vaccination
- increased knowledge in the NT, particularly in Central Australia, about ear disease and the effect of the vaccine on ear disease
- increased research capacity in the NT, particularly in Central Australia, which may have long-term benefits for other health problems
- strengthening collaborative relationships between health providers

*Potential disadvantages*

- possible confusion between the routine childhood vaccination system and the SB vaccine trial, with the danger that coverage of routine childhood vaccination may fall
- difficulties and potential confusion for routine vaccination providers and parents if an alternative pneumococcal vaccine is introduced before the recruitment phase of the trial is completed
- the possibility that unexpected side-effects of the vaccine may occur
possible criticism of health services from the anti-vaccination lobby or other
groups for being involved in a project that is ‘experimenting’ on NT children.

2.5 Logistic and resource considerations

The initial proposal was for a trial offering the SB eleven valent conjugate pneumococcal
vaccine to all children aged 2-23 months at the commencement of the trial, and all children
born during the following three years, throughout the NT.

The feasibility study found that this option is not feasible because:

- such a project is of too large a scale to be resourced and managed successfully,
given the current research infrastructure and experience in the NT. This option
would require over fifty staff – it is unlikely sufficient experienced staff could be
recruited here or from interstate and retained for the life of the project. Regular
visits (every eight weeks) would be required to 97 remote community health
centres, with communication in many different Aboriginal languages, for over
three years. It is unlikely that such a large number of study sites could be
managed successfully.

- the estimated cost of this option is over twenty million dollars. After statistical
analysis of the number of children and duration of follow-up required to
reliably detect the reduction in IPD that is expected from the vaccine, it was
found that the scale of the study design could be reduced considerably. The
design was modified to be conducted only in Central Australia (and possibly
the Tiwi Islands) and to recruit newborn children for only two years instead of
three. Central Australia was chosen because the disease is much more common
there and because there was a greater level of support for the trial there.

Logistical issues and costs were assessed in Central Australia based on this modified
design. While considerable difficulties were identified during consultation and development
of implementation plans, the feasibility study found that this design could be successfully
implemented.

The estimated cost of this design was $A10-11 M, approaching feasibility for the sponsor.
This is approximately 15 per cent higher than SB indicated they had allocated for this
project, but this could probably have been resolved after refinement of implementation
plans and cost estimates in the final funding negotiations with SB.

In June 1999 the feasibility study became aware that Prevenar™, a seven-valent conjugate
pneumococcal vaccine manufactured by Wyeth Lederle, would very likely be introduced as
a routine childhood vaccine in the second half of 2001. This would have a major impact
of the trial. The potential impact of Prevenar™ was investigated in detail, and further
consultation on this issue undertaken with THS policy officers and health services in Central
Australia. There was considerable support to conduct the trial despite the introduction of
Prevenar™, particularly from Central Australian health services. However, the feasibility
study team determined that there was a high risk that the study would not be successfully
completed after Prevenar™ was introduced, and that the trial should not be commenced in
this environment (see below).

Alternative design options to avoid a long period of overlap with Prevenar™ were considered.
This required a shorter recruitment period (preferably completed by December 2001) and
reduced geographic scope so that the trial could commence in January 2001. The more
communities that were involved in the trial the longer it would take to commence the trial
in all communities.

As a consequence of these restrictions, IPD could no longer be the primary outcome
measure of the trial. Even though IPD is much more common in Central Australia than
elsewhere, it is still an uncommon event and was felt to require a large trial conducted over
two years to assess whether the vaccine has definitely reduced the number of IPD cases.

Lower respiratory tract infections and ear disease are much more common illnesses caused
partly by pneumococcus. A fall in these diseases may be confirmed much earlier than a fall
in IPD. It is possible to recruit children for only one year (including children up to age five
years) into a trial which assessed the effectiveness of the SB vaccine on these outcomes.
This considerably reduced the risk that the early introduction of Prevenar™ would cause the trial to be abandoned. IPD cases would be measured during this trial, but would not be one of the primary outcome measures.

The modified design developed to meet these criteria focused on otitis media and pneumonia as the primary outcome measures. The trial was planned to be conducted in three areas in Central Australia and the Top End, involving children aged up to five years at the commencement of the study and children born over the following twelve months.

The interim report to the CRCATH Board in August recommended that a trial focusing on IPD as the primary outcome measure should not proceed, but that the small scale trial focusing on pneumonia and otitis media should be fully developed and proposed to SB. The Board accepted this recommendation. This design was developed further, including review by the feasibility study’s International Advisory Committee, and a protocol synopsis and detailed cost estimate submitted to SB in mid-September.

Details of the evolution of the scientific design of the project are included in Section Three. Details of the major logistical issues that were considered are included in Section Four.

2.6 Consultation

The consultation program was targeted at four groups of people:

- health policy officers and health service managers;
- health professionals, particularly those involved in childhood vaccination programs;
- community organisations including Boards of community controlled health services and organisations with an interest in child health; and
- parents

The consultation program commenced in Darwin and Alice Springs, and progressed to other urban centres. Preliminary contact was made with health services in remote communities but further consultation was postponed when major changes were made to the design and scale of the proposed trial as the feasibility study progressed. Consultation was well advanced in the Top End when the decision to focus the trial in Central Australia was made – further consultation in the Top End did not proceed, other than advising all people already contacted of the change of direction.

Extensive consultation was undertaken in Central Australia with urban-based organisations in Alice Springs and Tennant Creek, and a consultation program to sixteen remote communities commenced. However, only four communities had been consulted when the third major change to the design and scale of the proposed trial occurred. This reduced the trial to only three areas, only one of which was in Central Australia. At this point the consultation program in Central Australia was stopped, other than informing people of the basic issues which caused this change of direction.

After the August decision of the CRCATH Board that only a small-scale trial in three areas would be considered, minimal further consultation was conducted until the details of this trial design were completed. Thereafter consultation was restricted to progress reports to the areas potentially involved, pending the response to the final proposal from SB. The consultation program during the feasibility study had been quite extensive, including up to five meetings with some organisations.

Conducting further consultation in communities before a final decision on whether the trial would proceed was deemed to be inappropriate. In the Top End there was general interest in and support for a trial. Confirmation of definite support depended on clarification of issues such as final implementation plans, effects on existing service provision and evidence of the safety of the vaccine.

However, there was some serious suspicion of the proposal and in some cases serious hostility, particularly in Darwin Community Care Centres, although after further discussion of major issues the degree of suspicion was considerably reduced.
In Central Australia a greater level of support, and in some cases enthusiasm, was found for the trial. There were the same requirements that issues of safety and practicalities of implementation be clarified before final agreement to be involved in the trial would be given. However, the overall level of support from AMSs and THS senior managers and health professionals was sufficient to enable the trial to proceed.

Details of the consultation program are included in Section Five.

2.7 Informed Consent

A very promising model of communicating the necessary information about the trial to both Aboriginal organisations and individual parents had been identified and assessed. This model was based on the award-winning information materials developed for the rheumatic heart disease prevention project. It includes the following elements:

- an illustrated booklet in English explaining the participant information. The booklet would be provided to all parents. Written documents would not be translated into Aboriginal languages, which are oral not written languages.
- graphical flip-charts to be used during the personal explanation by research team members or liaison staff. The information in the booklets would be translated into Aboriginal and migrant languages to be used with the flip-charts for personal explanation by liaison staff fluent in these languages.
- a video, with voice-over translated into appropriate Aboriginal and migrant languages.

These information materials would be used in an integrated community consultation and individual parent information and consent process.

Preliminary assessment of these types of materials with experienced community research staff and individual community members (parents and grandparents) indicated that the formats chosen were the most appropriate available.

The study team was confident that an integrated community consultation and individual parent information and consent process, using the identified formats for information materials, was the best available approach and will be effective in adequately communicating with almost all parents.

However development and testing of specific community consultation and informed consent processes had not yet been conducted. It was planned to commence this work during the feasibility study, but delays in recruiting staff and the inability to find a suitably experience social scientist to undertake this work severely limited progress in this area. Development and testing of an informed consent process will have to be undertaken during the preparatory phase of the trial.

Full details of the informed consent process are included in Section Six.

2.8 Estimated cost

The initial estimated cost of the initial design proposal (all NT children for three years) was in excess of $A20 million, in excess of what was acceptable to the sponsor. The initial estimated cost of the Central Australian (+/- Tiwi) option was $A10.1 million. However, as the potential impact of Prevenar™ on the trial was investigated this design option was eliminated.

The initial cost estimate of the final design proposal was $A6.6 million.

2.9 Prevenar™

Prevenar™ was expected to be licensed in Australia by February 2001 and on the Australian market by approximately May 2001. This vaccine is very expensive, and could not be generally available unless the Commonwealth Government funded its introduction, probably only for high-risk children in the first instance. High-risk children would certainly include Aboriginal children in the NT, and possibly all children in Central Australia.
It is highly likely that Prevenar™ vaccination will commence in the NT before the end of the trial, probably in the second half of 2001. The feasibility study became aware of the likely timing of the introduction of Prevenar™ after the decision to focus the proposed trial in Central Australia. If an actively promoted Prevenar™ vaccination program commenced in Central Australia during the trial, health services would find it very difficult to promote Prevenar™ vaccination at the same time as facilitating a trial of the SB vaccine.

Individual consultations with THS and Central Australian health services on whether the trial should proceed, despite the likely introduction of Prevenar™, were inconclusive. There was individual support for the trial, but crucial organisations, particularly THS, wanted to hear the views of senior representatives of all relevant organisations discussed in the one forum, and confirmed officially by the governing bodies of each organisation.

To this end, a workshop was convened in Alice Springs on 11 August. This was the last opportunity to make progress on a unified commitment before the CRCATH Board meeting of 16 August. As the feasibility study was due to be completed by 5 September, there were no further options to pursue this united commitment. Senior representatives of almost all relevant organisations confirmed attendance, but not all were able to attend on the day. The workshop was not able to reach a firm consensus. While support for the trial remained, the result was inconclusive – certainly the required united commitment was no further advanced.

There was insufficient time left to the feasibility study to conduct further negotiations to determine whether such a united position could be achieved. On this basis, the feasibility study recommended to the CRCATH Board that the large-scale Central Australian trial proposal should not proceed.

2.10 Outcome of the feasibility study

The interim report of the feasibility study to the CRCATH Board on 16 August 2000 recommended that:

- a large-scale trial of the SB vaccine with IPD as the primary outcome measure should not proceed, principally because of the difficulties posed for the trial by the likely introduction of Prevenar™; and

- a smaller-scale trial with ear disease and pneumonia as the primary outcome measures be fully designed and proposed to SB.

The Board accepted these recommendations and the feasibility study team spent the last few weeks of the study developing and costing this smaller-scale design. The final study proposal was submitted to SB in mid-September.

The scientific design of the study has been modified considerably from that originally proposed. The final design assesses the effectiveness of the vaccine on two very serious and common health problems in the NT, pneumonia and ear disease. The health research capacity in the NT is well suited to conducting this trial, both in terms of expertise in these areas and in capacity to undertake a clinical trial of this scale. The consultation program determined that there is considerable support from health policy makers and health services in both the Top End and Central Australia to conduct this trial.

Although Prevenar™ will probably be available in the NT by the end of 2001 there is good reason to assess the effectiveness of the SB vaccine. The SB vaccine contains four more serotypes of pneumococcus, which may prevent about 10 per cent more cases of IPD. The SB vaccine also contains a Haemophilus protein which may make it more effective at preventing otitis media.

On 6 October the Medical Director of SB Australia advised the Director, CRCATH that the modified proposal had been accepted by the company and the project would be funded.
3. Scientific design

The original proposal for a clinical trial of the SB eleven valent conjugate pneumococcal vaccine in the NT was to offer the vaccine to all children aged under two years, and all newborn children born for the following three years. The trial was to be conducted largely through the existing childhood vaccination system administered by primary health care services (CHCs, AMSs and GPs). The primary outcome measure was to be IPD.

There are approximately 3,600 children born each year in the NT. This proposal would have included all children born over a five year period (those born two years before the project started and for the three years of the project). Approximately 18,000 children and their parents would have to be approached about being in the trial, and if only 70 per cent actually enrolled in the trial there would be over 12,000 children recruited.

During the feasibility study several major obstacles were identified which made it unlikely that the project could be successfully carried out as originally designed. Several major changes were made to the scientific design during the feasibility study to avoid these problems. These changes were made in consultation with senior scientific staff of SB and with the Director and/or Board of the CRCATH. The major issues identified, and the design changes in response to these issues, are summarised below.

<table>
<thead>
<tr>
<th>Study Design, Version One</th>
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<tbody>
<tr>
<td><strong>Geographic scope</strong></td>
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<tr>
<td><strong>Recruitment</strong></td>
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<tr>
<td><strong>Principal outcome measure</strong></td>
</tr>
<tr>
<td><strong>Implementation strategy</strong></td>
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3.1 Implementation through routine vaccination system

Feedback from primary health care providers, both urban and rural, indicated that the trial could not be implemented through the routine childhood vaccination system. Primary health care staff, particularly Community Health Nurses (CHNs), did not support being directly involved in a clinical trial for several reasons:

- there would be an increased workload and they were not confident that additional resources provided to conduct the trial would be adequate;
- in some urban community health centres there did not appear to be adequate space for additional staff, storage and work areas; and
- CHNs were reluctant to become involved in a research project. The view was expressed by some that this could compromise their relationship with mothers and families.

It also became apparent during consultations that, with the large number of vaccine providers involved, considerable training and quality assurance monitoring would be required throughout the trial to ensure adequate community consultation, informed consent, monitoring and documentation. Maintaining adequate research standards would be difficult because of high staff turnover and low numbers of children enrolled at each CHC, particularly in remote areas.

Within several weeks of starting the feasibility study it became apparent that the trial would have to be implemented by research staff who were mostly independent of the existing childhood vaccination system. However, it would be essential that the research staff and primary health care staff cooperated closely, for both the success of the trial and to support the routine childhood vaccination system.
The trial proposal was redesigned to be implemented by teams of research staff working in the five urban centres (Darwin, Nhulunbuy, Katherine, Tennant Creek and Alice Springs). Mobile teams based in these five service centres would visit remote communities on an eight-week cycle.

### Study Design, Version Two

<table>
<thead>
<tr>
<th>Geographic scope</th>
<th>NT-wide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>children aged up to two years at the commencement of the trial and newborns for the following three years</td>
</tr>
<tr>
<td>Principal outcome measure</td>
<td>invasive pneumococcal disease</td>
</tr>
<tr>
<td>Implementation strategy</td>
<td>the trial would be conducted mostly by research staff based in urban areas with mobile teams making regular visits to remote communities</td>
</tr>
</tbody>
</table>

### 3.2 Size and complexity, including geographical dispersion

The feasibility study team then investigated an implementation plan based on research staff performing most aspects of the trial, either at permanent urban sites or as mobile teams visiting remote communities and working from CHCs while in each community.

This approach would involve research staff vaccinating children at approximately 120 study sites. These sites consisted of over 90 remote CHCs, five urban AMSs, nine urban CHCs and approximately ten GPs. This would require nine or ten mobile teams of two people with part-time staff in each large community. The study would have to cooperate closely with the routine childhood vaccination program in each of these sites.

Approximately fifty research staff would have been required for this study. Recruiting and training this number of staff may not have been possible. Staff turnover would have become a significant problem, raising problems of maintaining high research standards. Maintaining good cooperation with CHC staff in so many sites and good communication with so many communities would have been very difficult and require considerable management resources. Initial cost estimates of this approach were prohibitively expensive.

As these problems became apparent, the trial design was revised again. Statistical analysis was undertaken of the necessary number of children required to demonstrate the expected reduction in IPD. This indicated that the number involved in the original proposal was considerably more than needed. As the disease is far more common in Central Australia (66 per cent of cases of IPD occur there) statistical calculations were done to ascertain the number of Central Australian children required to demonstrate the effect of the vaccine. This indicated that vaccinating Central Australian children up to age two years, and newborns for the following two years (instead of three as originally proposed), could be expected to include sufficient children to reliably demonstrate the effectiveness of the vaccine.

A smaller, shorter trial has a greater chance of being successfully completed. The greatest benefit from the vaccine would occur for Central Australian children who have a higher risk of disease than Top End children. For these reasons it was decided to reduce the scope of the proposed trial to Central Australia only. The Tiwi Health Board (THB) had expressed considerable interest in being involved in the trial, so the option was left open to include the Tiwi Islands in the trial pending further negotiations. The feasibility study team therefore changed direction to focus on Central Australia after seeking direction from the Director, CRCATH and several Board members, and members of the International Advisory Committee.
**Study Design, Version Three**

<table>
<thead>
<tr>
<th>Geographic scope</th>
<th>Central Australia (+/- Tiwi Islands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>children aged up to two years at the commencement of the trial and newborns for the following two years</td>
</tr>
<tr>
<td>Principal outcome measure</td>
<td>invasive pneumococcal disease</td>
</tr>
<tr>
<td>Implementation strategy</td>
<td>the trial would be conducted mostly by research staff based in urban areas with mobile teams making regular visits to remote communities</td>
</tr>
</tbody>
</table>

### 3.3 Prevenar™, an alternative conjugate pneumococcal vaccine

Another pharmaceutical company, Wyeth-Lederle, has produced a similar vaccine (Prevenar™) which is a conjugate vaccine containing seven pneumococcal serotypes. The SB vaccine contains eleven serotypes and may also offer protection against *H. influenzae*. The SB eleven valent vaccine is likely to be 5–15 per cent more effective than Prevenar™ at preventing pneumococcal meningitis and pneumonia because of the additional four serotypes in the SB vaccine. The additional serotype coverage and the *H. influenzae* protein in the SB vaccine may also make it more effective at preventing ear disease and may offer additional protection against pneumonia.

Prevenar™ was thought likely to be licensed and on the market by the middle of 2001, but not to be generally available until funded by the Commonwealth Government and introduced into the routine childhood immunisation schedule in the NT. This was anticipated probably to occur in the second half of 2001.

The Central Australian vaccine trial would probably still be in the first year of recruitment at the time Prevenar™ was introduced as a routine childhood vaccine. This would have a major impact on the trial. The trial could continue to recruit children after its introduction, but all parents would have to be advised that a licensed, recommended vaccine was available, and that the reason to enroll their child in the trial is because the SB vaccine may be more effective. Theoretically, the case that the SB vaccine may be more effective is reasonably strong and many parents would have chosen the SB vaccine. However, the introduction of Prevenar™ would reduce the number of parents who enrolled their children in the trial – the degree of this reduction could not be estimated.

The introduction of Prevenar™ would also have made the conduct of the trial more difficult in several ways:

- the informed consent process would be more complicated as parents would then have to be informed about two vaccines and the differences between them;
- coordination with the routine vaccination system would be more complicated and there would have to be frequent checks as to which vaccine each child was due to receive (ie, whether enrolled in the trial or due for the routine vaccine); and
- there may be public criticism of the research project and health services who were cooperating with the project about conducting a research project on children with an unlicensed product when a licensed product was available.

If an active Prevenar™ vaccination program commenced in Central Australia during the trial, health services would find it very difficult to promote vaccination and facilitate a trial of the SB vaccine at the same time. This would pose a major problem for the trial – it may not be possible to complete once Prevenar™ in introduced. If there was a major risk that the trial would not be successfully completed, it should not commence.
For the trial to proceed, there would have to be a commitment from most, if not all, service delivery organisations in Central Australia and THS to complete the trial despite the introduction of Prevenar™. It would be much easier for health services and THS to support such a delay if data on the reduction in pneumococcal disease during the first year of the trial were available before Prevenar™ vaccination commenced. At the end of the first year this reduction would probably not have reached statistical significance, but provided it was heading in the right direction there may have been general support in Central Australia to delay an active Prevenar™ campaign for up to twelve months until the trial was completed.

However, it appeared likely that Prevenar™ vaccination would commence in the NT before sufficient outcome data would be available from the trial. A risk analysis of progress with the trial and Prevenar™ availability estimated that there was only about a 20 per cent likelihood that outcome data would be available (Appendix B). There could be a delay of up to eight months. The essential issue for service delivery organisations in Central Australia was thus whether they were prepared to:

- delay commencement of an active Prevenar™ vaccination campaign for up to eight months before the first progress report of outcome data was available from the trial; and then
- delay active Prevenar™ introduction again by up to nine months on the basis of progress report data.

Consultation with senior policy makers in THS and health service representatives in Central Australia in August on this issue found that there was individual support to commence the trial and continue it to completion after the introduction of Prevenar™.

However, there was also recognition by most people consulted that the trial would only be successfully completed if there were an unequivocal collective decision to continue the trial after the introduction of Prevenar™. This collective agreement required considerable negotiation between senior representatives of a range of organisations. The final agreed position would also require endorsement of the governing bodies of these organisations.

Although consultation with individuals indicated that this collective agreement may have eventually been possible, it could not be negotiated before the August meeting of the CRCATH Board, which was the deadline by which the future of the proposed trial had to be decided. Furthermore, negotiation to obtain this collective agreement could have taken a further four to twelve weeks, with endorsement of the governing bodies of each organisation taking another eight to twelve weeks. The longer the decision to proceed with the trial was delayed the longer the start date of the trial would be delayed, and the closer the start date of the trial came to the likely introduction of Prevenar™ which compounded the problems for the trial.

It was apparent that continuing to proceed with the two-year Central Australian trial proposal was a very high-risk option. The feasibility study therefore recommended to the August meeting of the CRCATH Board that this proposal be abandoned, but that a modified trial proposal be further developed and, if found to be scientifically sound, submitted to SB for funding. This modified trial would assess the effectiveness of the SB conjugated pneumococcal vaccine on pneumonia and otitis media in a smaller number of children, with a one-year recruitment period only. The Board accepted these two recommendations.

### 3.4 Possible Study Comparing Effectiveness of SB Vaccine Versus Prevenar™

A direct comparative trial of the effectiveness of the SB and Wyeth vaccines was considered, as this is a scientific question with very important policy implications. It would be possible to conduct a trial that directly compared the effectiveness of the two vaccines. Such a trial would have to be a randomised trial, in which parents were offered one of the vaccines but could not choose which particular one. Outcome measures would be lower respiratory tract infections and ear disease – the difference in IPD cases in the two groups would be too small to measure reliably in a small population in a short period of time.
Initial indications are that approximately 2,000 children (1,000 receiving each vaccine) would be needed to demonstrate differences between the two vaccines. This trial would increase the complexity of informed consent and vaccine administration and would require a large number of children. The feasibility study did not investigate this option in detail because it was considered to be more complex than any of the other alternatives considered, and thus likely to be more difficult and expensive, and less likely to be successfully completed.

3.5 The final scientific design: A respiratory and ear disease effectiveness study

**Study Design, Version Four**

<table>
<thead>
<tr>
<th>Geographic scope</th>
<th>Three areas in Central Australia and the Top End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>children aged up to five years at the commencement of the trial and newborns for the following nine to twelve months</td>
</tr>
<tr>
<td>Principal outcome measure</td>
<td>ear disease and pneumonia (confirmed by x-ray)</td>
</tr>
<tr>
<td>Implementation strategy</td>
<td>the trial would be conducted by research staff visiting remote communities on a regular basis and local liaison/research staff</td>
</tr>
</tbody>
</table>

The incidence of IPD is the outcome measure that is most specific to assessing the effectiveness of the pneumococcal vaccine, as it is a direct measure of disease caused by pneumococcus, particularly if disease caused by specific serotypes is measured. However, even though IPD is much more common in Central Australia than elsewhere, it is still an uncommon event and requires a large trial conducted over two years to assess whether the vaccine has definitely reduced the number of cases.

Pneumonia and otitis media are much more common illnesses caused partly by pneumococcus. It is expected that a fall in these diseases may be confirmed much earlier than a fall in IPD. However, the proportional reduction in occurrence of these diseases will be less than for IPD, as many cases of both pneumonia and otitis media are caused by other organisms which will not be directly affected by the pneumococcal vaccine. In addition, evidence to date for Prevenar™ indicate that the effect of conjugate pneumococcal vaccines on pneumonia, and particularly otitis media, is less than the effect on IPD.

These two factors (more common diseases as outcome measures, but a smaller effect of the vaccine on these outcome measures because of other causes of these diseases) have an opposite effect on the number of children required for a study focusing on pneumonia and otitis media as the primary outcome measures, compared to a study focusing on IPD. Fewer children would be required to study a more common condition, but more children would be required if the expected effect were smaller.

**Sample size calculations**

For ear disease, the prevalence of eardrum perforation was chosen as the primary outcome measure. The minimum sample size required in each group of children aged 6-14 months (unvaccinated and fully vaccinated) is 91. This is based on a study with 80 per cent power to detect a 50 per cent difference in prevalence of perforation between vaccinated and unvaccinated children, where the baseline prevalence of perforation is 40 per cent.
For pneumonia, the incidence of x-ray confirmed pneumonia in hospitalised children was chosen as the primary outcome measure. Based on unpublished data from Central Australia, the minimum incidence of hospitalised x-ray confirmed pneumonia in Aboriginal children aged under five is 0.068 per child-year. The minimum sample size required to detect a 50 per cent fall in incidence to 0.034 per child-year with 80 per cent power is 693 after one year of observation, or 346 after two years of observation.

These sample size calculations indicated that a study focusing on pneumonia and otitis media would require a smaller number of children and a shorter recruitment period than a study focusing on IPD as the primary outcome measure. Moreover, the effect of the vaccine on these two conditions is a very important research question here. These are very common and serious diseases in NT children, but very little research has been conducted elsewhere on the effect of the vaccine on these health problems, while considerable research has been conducted on the effect on IPD.

The study design was therefore modified to recruit children for only one year (including children up to age five years) into a trial that would assess the effectiveness of the SB vaccine on pneumonia and otitis media. This would considerably reduce the risk that the early introduction of Prevenar™ would cause the trial to be abandoned. IPD cases would be measured during this trial, but would not be one of the primary outcome measures.
4. Logistics

The proposal for a vaccine effectiveness trial that aimed to recruit all NT newborns for three years, and all children under two years of age at study start, was unique with respect to previously conducted research in the NT. It was the first clinical trial of that scale ever proposed for the region, and the first that would have necessitated the involvement of the entire spectrum of health service providers.

The feasibility study commenced with only a broad outline of a scientific design. The aim of the design and logistics program was to refine this design, develop a rigorous scientific protocol, devise implementation plans and cost the trial. The scope of the program did not include the development of detailed operational manuals. It was envisaged this would occur during a preparatory phase if approval were given for the trial to proceed.

Given delays in recruiting staff to the project, several major changes to the study design and as the scientific protocol was not completed by the end of the feasibility study period, there were aspects of the proposal that had not been fully assessed and many issues remained unresolved. This section of the report details the work that was done to the end of the feasibility study. It outlines areas that require further work for alternative study designs, and provides recommendations on design and logistics issues that are relevant to future proposals for large-scale clinical trials in the NT.

4.1. The design & logistics process

The scientific and operational design of this trial was a collaborative effort between a large number of individuals and organisations (Appendix C). The scientific protocol was developed cooperatively by the feasibility study team, SB, professionals within several organisations and an International Advisory Committee consisting of experts in vaccine trials and pneumococcal disease. Implementation plans, which accommodated all settings in which vaccines are delivered in the NT, were proposed and their feasibility assessed through a combination of qualitative and quantitative methods including discussions with service providers, surveys, review of existing protocols and literature, and feedback from the consultation team. These plans, and the scientific protocol, were addressed according to eight categories:

- subject recruitment: community and individual information campaigns; identification of eligible children;
- vaccine delivery: immunisation of children;
- vaccine supply: distribution, storage, cold chain management and vaccine accountability;
- data management: collection, storage and analysis;
- outcome assessment: adverse events, primary and secondary endpoints;
- staffing and human resource requirements: recruitment and training;
- study management;
- intellectual property;
- equipment and supplies; and
- study budget.
4.2 Scientific design

The initial design was an effectiveness study using historical controls with a primary endpoint of IPD. Rates of disease before and after vaccination would have been compared using existing THS data. IPD remained the primary endpoint until the decision to reduce the scale of the study to only a few communities was made in late August. Secondary endpoints considered over time included:

- radiologically obvious pneumonia in hospitalised children;
- otitis media and tympanic membrane perforation;
- carriage of *S. pneumoniae* and non-capsular *H. influenzae*;
- community diagnosed respiratory illness and antibiotic use;
- immunogenicity studies; and
- serious adverse events and vaccine reactions.

The proposed vaccine schedule for infants and toddlers was as follows:

- newborns: 2, 4, 6 & 18 months of age
- 2 - 6 mth olds: as per newborn schedule, doses 2 months apart
- 7 - 11 mth olds: two doses, two months apart + booster
- 12 - 23 mth olds: two doses, two months apart

The minimum interval between doses is 21 days. Throughout the feasibility study, the potential to include children up to five years of age in the catch-up program remained an important consideration. If included, these children would most likely receive two doses of the vaccine.

Expected and assumed outcomes of the trial were calculated using existing NT IPD surveillance data, clinic surveillance systems in some remote communities, data from existing studies in the NT such as those from the Ear Health and Education Unit of the MSHR, and published data from studies of the Wyeth-Lederle 7 valent vaccine (Prevenar™).\(^{15}\)

4.3. Recruitment

As outcomes of the trial were calculated assuming coverage rates of 70 per cent in the non-Indigenous population and 80 per cent in the Indigenous population, the recruitment process would have needed to be intensive. Recruitment was initially proposed to continue for three years from study start date, however this was reduced to two years following initial cost estimates, and review of the sample sizes required to detect statistically significant outcomes.

For parents to make an informed decision, adequate information needed to be supplied in a manner which enabled them to consider the issues in their own time, and in an environment in which they felt comfortable. Given time constraints in clinical settings, and the complexity of the consent process, it was not considered sufficient to wait until the child presented for their routine immunisations to provide information about the trial.

4.3.1 Methods

Discussions were held with the senior staff of maternity units and maternal and child health services throughout the NT. Information on avenues for accessing antenatal and postnatal women was collated, and the experiences of vaccine trials elsewhere were considered.\(^{16}\) In addition, issues considered important for improving immunisation coverage were examined in the medical literature.\(^{17-20}\)
4.3.2 Results

4.3.2.1 Community information

Community information, consisting of both media campaigns and information sessions, would be needed prior to the first child being vaccinated. These campaigns were found to be particularly useful in studies in the US, as field workers indicated it was easier to recruit participants when they had heard about the project before they were spoken to.\(^\text{16}\)

Initial contact with parents could be made in antenatal clinics. This could be a brief visit to raise awareness of pneumococcal disease, the vaccine and the study. Written and/or pictorial material could be provided. Additional avenues for raising awareness include periodically establishing information booths in shopping centres in urban areas and distributing both audiovisual and printed material to community groups and health services throughout the NT.

In remote communities, mobile teams could be responsible for conducting community and parent information sessions in locations to be determined by the teams prior to the first visit. Individuals could be accessed at home and/or through women’s groups and/or community centres. More detailed assessment of information provision in remote communities was planned by the consultation team during the preparatory phase.

4.3.2.2 Newborns

Approximately 97 per cent of births in the NT occur in either one of the five THS hospitals or the Darwin Private Hospital (DPH).\(^\text{21}\) There are on average 220 births per month in Darwin (including DPH), 70 per month in Alice Springs and 30, 15 and 3 per month in Katherine, Nhulunbuy and Tennant Creek respectively. Trial staff could contact each unit daily to capture new births, provide preliminary information to parents in the postnatal period and obtain permission to contact the family at home.

At approximately six weeks post discharge, trial staff could visit the family at home to provide detailed information and obtain approval to enrol their child. An appointment/referral could then be made for the child at their chosen immunisation provider. Formal consent would not have been obtained until the first immunisation encounter, effectively providing a time for parents to consider their options. Staff in each of the maternity units indicated this arrangement would not have created any particular difficulties, and offered several suggestions for targeting antenatal women.

To ensure all newborns were captured, data from the NT Births, Deaths and Marriages register could be downloaded fortnightly from the Business Information Management Unit (BIM) at THS. This would require all women admitted to hospital for confinement providing written consent for release of this information to the researchers. If children were identified that were not captured prior to discharge, letters could be sent informing parents of the trial, then followed up with a phone call and/or home visit.

The study could capture those children not born in the Northern Territory at the time of first presentation for immunisation.

4.3.2.3 Catch-up

Using current immunisation registers, letters could be sent to parents of all eligible children informing them of the trial, followed up by phone contact to arrange either a home visit, or to meet them at the time their child’s next immunisation was due. Families without telephones including those in remote communities could be visited at home with the assistance of local liaison staff.

All NT resident children who have been previously immunised can be identified through either the NT Childhood Immunisation Register (NTCIR) or through the Australian Childhood Immunisation Register (ACIR). The former will not capture any child born outside of the Northern Territory who has not been immunised, and use of ACIR is problematic due to access difficulties and incomplete or incorrect Medicare details. Recent data indicate there is a discrepancy in coverage estimates of approximately 7 per cent, with the NTCIR data higher than those of ACIR (Christine Selvey, THS, personal communication). A particular advantage of the NTCIR is that all children in the dataset are provided with a THS health record number (HRN), providing links to hospital separations data and the new Community Care Information System (CCIS).
Access to, and use of, NTCIR data is regulated by formal agreements between service providers and the Centre for Disease Control. Use of the dataset during the trial would have required both ethics clearance and written agreement from the agencies contributing data (ie. THS, AMSs and GPs.)

Figure 1: Recruitment Process
4.3.2.4 Exclusion criteria
The following exclusion criteria applied for all study options. They would be checked at the
time of study entry and, if any applied, the child would not be enrolled:

- history of allergic disease or reactions likely to be exacerbated by any
  component of the vaccine;
- considered likely to leave the NT before completion of the primary vaccination
  course (i.e. within 4 months of the first dose of vaccine for those aged up to
  6 months, or within 2 months of the first dose for those aged 7 months to 5
  years);
- previous vaccination against *Streptococcus pneumoniae*;
- rectal temperature $\geq 38^\circ C$ (100.4°F), axillary temperature $\geq 37.5^\circ C$ (99.5°F),
opt oral temperature $\geq 37.5^\circ C$, tympanic temperature on oral setting $\geq 37.5^\circ C$,
tympanic temperature on rectal setting $\geq 38^\circ C$ if rectal thermometer or
tympanic thermometer on rectal setting is used; a temperature greater than or
equal to these cut-offs warrants deferral of the vaccination pending recovery of
the subject;
- other conditions that in the opinion of the principal investigator may potentially
  interfere with interpretation of study outcomes; or
- presence of an absolute contraindication to any of the routinely scheduled
  childhood vaccines, as described in the current (seventh) edition of *The
  Australian Immunisation Handbook*.

4.3.2.5 Monitoring recruitment
A recruitment tracking system could be developed in conjunction with SB to monitor
progress against the recruitment plan. The number of sites and the target number of
subjects to be enrolled per site could be collated using ABS population estimates, clinic and
community population registers.

Enrolment forms, provided by SB, could be completed weekly and faxed to SB to track
enrolment. Identifying information on these forms would be limited to study ID number and
site. Recruitment logs of all children enrolled by study site could be generated fortnightly by
the NT central office and returned to all sites/teams to facilitate tracking of children.

4.3.2.6 Monitoring person time at risk for non-study subjects
For IPD endpoints, there was a need to evaluate disease incidence prospectively in
vaccinated and unvaccinated children. It would therefore have been necessary to collect
some information on children who declined to be enrolled in the study to accurately
calculate person time at risk for unvaccinated children.

For those children who were not enrolled, parents could be asked to contact us, or grant
permission for the study team to contact them, at 6, 12 and 24 months to determine if they
had left the NT. This was more likely to be a problem for urban, non-Indigenous children,
particularly in Katherine and Darwin, which have large and mobile military populations.

4.3.2.7 Resource requirements for recruitment activities
One person could reasonably have been able to achieve at most 20 home visits per week
(30 minute visit plus 30 minutes travel time each visit) together with other recruiting
activities such as hospital visits and community information sessions. Therefore, the
minimum number of staff required for recruitment activities in each of the urban centres
equated to:

- Darwin - 4 in year one and 2 each recruitment year thereafter;
- Alice Springs - 2 in year one and 1 each recruitment year thereafter;
- Katherine - one for each year of the trial; and
- Tennant Creek and Nhulunbuy - incorporated into tasks of other staff.
These figures assumed that one person visited families at home. This model raised the potential for security concerns and staff may have been reluctant to go alone. If this were to be addressed, the number of staff would need to be doubled. A motor vehicle would have been required for each site (two for Darwin) as well as telephones, stationery and study information materials.

4.4 Vaccine Delivery

Immunisations are currently delivered in approximately 127 sites in the NT, including 96 remote clinics, nine Community Health Centres (CHCs), five urban AMSs and 17 GPs. Registered nurses and/or health workers in CHCs deliver over 95 per cent of immunisations in the NT. The role of GPs is expanding.

4.4.1 Methods

Proposals for vaccine delivery were developed for each clinical setting and discussed with managers and/or senior clinical staff. Details on clinic functions, immunisation services and maintenance of the cold chain were also collated.

4.4.2 Results

Direct contact was made with all CHCs and GPs, three AMSs and five remote clinics. Discussions with remote centres were limited due to the change in focus of the study in June. Information was supplemented by discussions with a number of health professionals with experience in health service delivery in remote settings.

Details on the procedures to be undertaken at each study visit were contained in the scientific protocol.

4.4.2.1 Community Health Centres (CHCs)

CHCs are THS facilities, which provide a broad range of community health services. There are nine centres in the NT and all provide free infant health services, including immunisations. Given the CHCs are the largest immunisation providers in the NT, the success of the trial was dependent on the ability to include them, or at least have their support for independent sites.

Given the workload of the larger centres, the proposed implementation plan was to employ full-time staff in the clinics with responsibility for all aspects of the trial. For Katherine, Nhulunbuy and Tennant Creek, the initial proposal was to engage existing staff with appropriate training and support.

4.4.2.1.1 Results

Darwin

There are five CHCs in Darwin Urban; three large clinics in Darwin City, Palmerston and Casuarina, and two very small satellite clinics at Karama and Nightcliff. An average of 1,800 infant health encounters (which include immunisations) occur each month, predominantly through Palmerston and Casuarina. Fifteen percent of these are for children identified as Aboriginal and/or Torres Strait Islander (Vera Outred, personal communication). The clinics are staffed by Maternal and Child Health Nurses (MCHNs), and vaccines are administered at the end of a complete infant health assessment. Reception facilities are relatively limited and children are not identified as presenting for immunisation on arrival. No centres take appointments and infant health services do not operate on Wednesdays. Karama is closed on Mondays.

Clinic space is limited in all settings, particularly at Nightcliff and Karama. With the possible exception of Casuarina, there are no offices available for trial administrative tasks or for obtaining informed consent in private. All centres indicated that sharing clinic space would be unacceptable due to the potential for breaches of confidentiality and interference during client consultations.
As identified in the consultation program, there was considerable reluctance for routine staff to be involved in the trial. It was felt it would undermine professional relationships with clients. Similarly, nurses were uniformly concerned about giving three injections at the one visit. Provider attitudes to multiple vaccinations, as opposed to parental perceptions, is well documented as a significant factor in missed opportunities for vaccination.\textsuperscript{19,23-25} It became clear early that implementing the trial through Darwin CHCs was not a feasible option. Open hostility within the clinics was considered a substantial risk to the trial, compounded by issues such as lack of space. Intensive negotiation with the centres may have resolved some of the issues, but this was no longer necessary following the decision to limit the study to Central Australia.

\textit{Alice Springs}

There is one large CHC located some distance from the CBD (Flynn Drive) and three satellite infant health clinics in Alice Urban. Flynn Drive conducts infant health clinics every day except Thursday and accepts both appointments and drop-ins. The satellites operate from neighbourhood centres one morning per week on an appointment basis only. All centres are staffed by MCHNs.

The clinics provide an average of 350 immunisations per month (includes children up to 15 years of age) and approximately 4-7 per cent of clients are identified as Aboriginal and/or Torres Strait Islander. Another 7 per cent are of non-English speaking backgrounds and they provide services to a large number of tourists. Infant health sessions at Flynn Drive operate from two small clinic rooms, but there is space available for consent and administrative procedures. Staff indicated they were willing to accommodate the trial in the centre however were not prepared to allow trial personnel perform routine immunisations. Further negotiations regarding the flow of children through the clinic were needed, but early discussions suggested centre staff may have been prepared to deliver the study vaccine if consent and data were managed by trial personnel. Given the numbers of children seen through the centre, a minimum of two staff for year one (to cover the catch-up period), and one for each year thereafter would be required.

\textit{Katherine}

The CHC is located directly behind one of the major shopping centres in Katherine. While the centre is open all week, infant immunisations are only provided by appointment at a Thursday morning clinic. Opportunistic immunisations are done rarely. There is one MCHN coordinator and the clinic delivers approximately 20 immunisations per week.

Clinical staff were supportive of the trial and willing to be involved with the proviso that additional administrative support was provided in the centre. There was adequate space for consent procedures and the clinic could also have provided a base for mobile teams for the Katherine region.

\textit{Nhulunbuy}

Infant health services in Nhulunbuy are provided by a single MCHN who operates from a small clinic room co-located with the local GP. The MCHN accepts both appointments and drop-ins and delivers approximately 10 immunisations per week. The clinic is closed on Fridays. There is no space for additional staff.

The MCHN indicated that given current workload, taking on duties relating to the trial would have been problematic in the absence of additional administrative support. Further negotiations may have resolved some of these issues, if not then alternatives for vaccinating children in Nhulunbuy would have been required.

\textit{Tennant Creek}

Infant health services in Tennant Creek are provided by a single MCHN who is co-located with other community services at Tennant Creek Hospital. The position’s duties include maintaining immunisation coverage for cattle station residents in the region. The MCHN prefers appointments but accepts drop-ins and delivers between 5-10 immunisations per week. Clinic space is shared with other services.

The current MCHN was keen to be involved in the trial and saw significant additional professional benefits with respect to research training and experience. She would have been prepared to manage all aspects of the trial with additional administrative support to assist with recruitment and follow-up tasks.
4.4.2.1.2 Discussion

CHCs in Darwin are not feasible locations for a clinical trial of the scale initially proposed and prior to the decision to limit the study, alternatives such as independent study centres were considered. A major influence on this decision was the considerable reluctance of existing staff to support the trial, which would potentially have jeopardised its success in the centres. Similarly the difficulties the trial presented to staff in Nhulunbuy, albeit possibly resolved with further consultation, necessitated consideration of other options for urban children in that region. The inability to provide an accessible location for immunising children, and increasing the number of immunisation visits a child had, would undoubtedly have impacted on recruitment.

The trial would, however, have been feasible in CHCs in Katherine, Tennant Creek and Alice Springs provided adequate resources, training and support were supplied.

Less than five percent of immunisations in the NT are provided by GPs, but there are concerted efforts in the major centres to expand. Both the Top End and CA Divisions of General Practice have employed immunisation coordinators to facilitate and monitor this process. It was important to involve GPs in the trial, particularly as they potentially provided an important option for implementing the catch-up programs in urban settings.

Almost all practices across the NT operate entirely on an appointment system. One practice in Darwin has recently established an immunisation clinic one morning per week at Casuarina. ACIR data is either forwarded directly to HIC or through the local CDC. All supply data to NTCIR.

Three options for implementing the trial in General Practice were considered:

Option 1

All aspects of the trial are conducted by practice staff; including recruitment, consent, vaccine supply and delivery and data collection under the guidance of the practice manager who would be nominated as a sub-investigator. Reimbursement would be as follows:

- Meetings and training: $110/hr for principals
  $55/hr for other GPs
  $25/hr for practice RNs
- Recruitment/vaccine delivery: $25 per study visit
- All necessary equipment and/or resources applicable to the trial would be supplied, together with regular contact and support from trial management.
- Trial payments would be in addition to, and not affect, ACIR payments or routine consultation fees.

Option 2

Trial clinics are established on a regular basis in the practice (eg. one-day per week) with trial staff and/or general practitioners implementing trial procedures. Recruitment officers would arrange for appointments to be made for parents to attend the practice on those days.

Option 3

Appointments are made for parents at the practice who are met at the scheduled time by trial staff who are then responsible for all aspects of the trial. Routine services / consultation would occur before trial procedures.

The preferred option was the first, as it would have facilitated combining both catch-up and newborn programs in the general practice setting, allow practices to have greater ownership of the trial process and minimise the need to accommodate trial staff in the practice.
4.4.2.1.3 Results - GP

Darwin

Of the 13 GPs in Darwin urban who provide immunisations, six were tentatively willing to be involved and all unanimously chose option one. Those who declined cited small client numbers (< 5 per month) and the recent establishment of their immunisation services as primary influences on their decision.

Alice Springs

Three practices in Alice Springs deliver immunisations. One indicated enthusiasm, the other tentative support and the last declined involvement citing small client numbers as the primary reason. The former centres are located strategically in the CBD and have the ability to accept new clients if required for the catch-up program.

Nhulunbuy

There is one GP co-located with the CHC. Small numbers of children are immunised by the practice and primarily occur opportunistically. The GP indicated a willingness to be involved and preferred option one.

Tennant Creek

The GP in Tennant Creek refers children to the CHC for immunisations.

Katherine

There is one GP clinic in Katherine, which declined involvement, citing consent issues - it was considered too laborious - and small client numbers (less than 10 immunisations per month)

4.4.2.1.4 Discussion - GPs

Tentatively, eight general practices in the NT indicated interest in being involved, with option one the preferred implementation strategy. Importantly, these practices were potential avenues for facilitating the catch-up campaign, hence reducing some of the load from CCCs. At least one medical officer from each practice could have been identified as site coordinators, and given the small numbers of children immunised by GPs, the cost of the trial in these settings would not have been significant.

Alternative arrangements would have been needed for those children who would normally have been immunised at a GP who was not participating in the study. As it was important not to remove routine immunisation from GPs, the only feasible alternative was to refer children to a participating CHC or study centre for vaccine. This would have necessitated extra immunisation visits and therefore impacted on recruitment.

4.4.2.2 Aboriginal Medical Services

Two options for AMSs involvement with the trial were proposed and discussed with clinical staff and/or practice managers. These entailed either study centre status as outlined in the GP proposal, or employing specific trial staff for the clinics. Clinical staff at Danila Dilba (Darwin) and Wurli Wurlinjang (Katherine) were not accessed by the time the decision to limit the study to Central Australia was made.

4.4.2.2.1 Results - AMSs

Central Australian Aboriginal Congress (CAAC)

CAAC is located in Alice Springs and staffed by five full-time and three part-time medical officers, and six clinic-based Aboriginal Health Workers. There are no RNs employed in the clinic, but a Public Health Nurse oversees the immunisation program in conjunction with an AHW who works with the under five year olds. The clinic is open seven days per week (8.30am to 8.00pm Monday to Friday, and 8.30am to 12.30pm on weekends) and accepts both appointments and drop-ins.

The clinic immunises approximately 15 children per week on both an opportunistic and recall basis. All personnel are actively involved in immunising children and encounters usually entail additional growth and development assessments.
The service indicated a willingness to be involved however detailed negotiations regarding the way the trial would operate were not concluded by the time the proposal for the Central Australia wide study was abandoned. It was felt likely that urban AMSs would have some role in assisting with measuring endpoints for any smaller studies.

**Miwatj**

Miwatj is located in Nhulunbuy and is staffed by 2.5 medical officers (usually one in the clinic at any one time) and two Aboriginal Health Workers. It is open Monday to Friday (8.30am to 4.30pm) and does not take appointments. One of the medical officers assumes responsibility for immunisations.

The clinic immunises approximately one child per week, primarily opportunistically. Most children in Nhulunbuy are serviced by the THS infant health clinic or accessed through Yirrkala and Marngarr clinics by AHWs. Given the small numbers of children immunised in this centre, staff felt no additional resources would be required other than teaching aids, and they would probably have little difficulty incorporating the trial into routine service delivery.

**Anyinginyi Congress**

Anyinginyi Congress is located in Tennant Creek and provides primary health care to the urban Aboriginal population of the Barkly region (up to a 100km radius of the town). It is open Monday to Friday, 8am to 5pm and does not take appointments. Four doctors, two registered nurses and eight Aboriginal Health Workers staff the clinic. Vaccinating children is generally the responsibility of either the nurses or doctors, and the immunisation program is coordinated by one of the medical officers. The clinic delivers approximately 12 immunisations per week.

The service indicated a willingness to participate, although they indicated they would have required an additional AHW for the clinic. This person would also have been utilised by the service to strengthen existing immunisation programs. The program could have been coordinated by one of the resident medical officers, and they had office space available to support all trial activities in Tennant Creek. As with CAAC, the relatively small numbers of children immunised each week would have necessitated incorporating other tasks into the role of any additional staff supplied by the trial.

**4.4.2.2 Discussion - AMSs**

Given the opportunistic nature of immunisations in AMSs, either trial staff based full time in the clinic or study centre status would be the only feasible means of conducting the trial in the services. However, given the relatively small numbers of children immunised each week, an additional full time staff member may not be a cost-efficient option unless other urban tasks (eg. home visits, recall activities) were incorporated into their role.

There was considerable opportunity for sharing of trial responsibilities between the AMS and CHC in Tennant Creek. A full time staff member based in each centre, or co-located, would have been sufficient to cover all trial activities, including recruitment, vaccine delivery, adverse event monitoring and outcome data collection in the area.

**4.4.2.3 Remote Area Clinics**

There are 96 remote area clinics (RACs) in the proposed study area (NT and Nganampa) managed either by THS, Aboriginal Community Controlled Organisations or Grant-in-Aid arrangements. They range from small single RN and AHW centres to large clinics with resident GPs. Most also provide services to surrounding outstations on a mobile basis. Some clinics are not readily accessible by road and in the wet season many Top End communities in particular are only accessible by air. Children are immunised either opportunistically or through recall systems generated locally or through the NTCIR.

The complexities of conducting research and achieving high immunisation coverage rates in remote communities cannot be underestimated. There are issues of population mobility, language barriers, differing community priorities, staff stability and workloads, and seasonal changes that affect service delivery in all settings. Of fundamental importance in achieving success in any undertaking is establishing trust and familiarity with the community.
Various options for conducting the trial in remote settings were considered. Each had differing degrees of reliance on routine existing staff; none eliminated participation by CHC staff completely.

**Option 1**

Mobile teams visit the community once every two months. The NT was organised into study areas based on travel routes and/or proximity to each other to account for child movement (Table 1). At most, two communities per week would have been accessed, with teams consisting of two clinical staff (RN or AHW) and a part-time local community person for liaison and coordination.

The advantage of this option was that it minimised any additional load on the clinic and the potential for confusion and error. The primary disadvantage of this option was that it was highly likely that not all children would been accessed during each visit and that opportunistic encounters would have been missed. Similarly, the ability to immunise a child concomitantly with routine vaccines was compromised. Given the study was an effectiveness trial designed to assess the effect of the vaccine on a population rather than individual basis, rigid adherence to the schedule was not essential. This did not mean however that every attempt should not have been made to adhere to the schedule, and concurrently every effort made to improve the timeliness of routine vaccines.

**Option 2**

Employ full time staff for each of the larger communities, who then have responsibility for the smaller communities in each of the study areas. Staff would have needed a motor vehicle supplied, and local community liaison officers would still need to have been engaged.

From a budget perspective, option two would only be marginally more expensive than mobile teams. The primary advantage of this option was immediate access to children in the largest centres, the development of relationships with the community, and additional staff to assist in community clinics during quieter periods. Disadvantages of this option were the lack of companions to travel with between communities, which may have raised some security concerns, and an obvious impediment would have been a lack of accommodation in the communities.

**Option 3**

A senior and stable health professional in the community is engaged as a site coordinator (eg. resident doctor or RN) and existing community staff do all the work associated with the trial. Proposed reimbursement for their participation was follows:

- meetings and training: $110/hr for principals
- $25/hr for additional clinic AHWs or RNs; and
- consent/vaccine delivery: $150 per child fully vaccinated, or
- $60 for consent/dose one and $30 per subsequent study visit

All necessary equipment and/or resources applicable to the trial would have been supplied, with regular contact and support from trial management and mobile teams. The latter would still have been required to visit the communities on a regular basis to provide ongoing training, support and assistance with locating and vaccinating children.

**Option 4**

Mobile teams are responsible for community consultation, the consent process and vaccine dose one, then routine clinic staff become responsible for doses 2-4. Payments for training, meetings and study visits completed would have been as outlined above. Alternatively, clinics may have chosen to be reimbursed indirectly through the purchase of clinic equipment and/or community resources.
4.4.2.3.1 Results - RAC

By the end of the feasibility study, only five communities in the NT had been visited and each had had one general information session only. Detailed discussion of proposed implementation plans did not occur so we are unable to make an adequately informed decision on the feasibility of the proposal in these areas.

Early indications suggested the only acceptable option to some clinics would have been the provision of staff to do the majority of work, particularly the catch-up program. This meant that either options 1, 2 or 4 may have been the only acceptable means of vaccine delivery, with option 4 possibly the only feasible method.

Feedback from the consultation team indicated the reasons for staff hesitation included:

- heavy existing workloads;
- reluctance to give an unlicensed vaccine to infants; and
- concern regarding their relationship with the community in the event something went wrong.
Table 3: Remote Community Study Areas by number of communities, distance, resident doctors and eligible children.

<table>
<thead>
<tr>
<th>Area</th>
<th>No. Com</th>
<th>Kms*</th>
<th>Catchup</th>
<th>Babies &lt; 2yr olds /2mths</th>
<th>Doctors</th>
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<td>Darwin</td>
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<tr>
<td>Tiwi/Croker/ Warruwi</td>
<td>7</td>
<td>Flights</td>
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<td>Arnhem Hwy - Murgunella</td>
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<td>501</td>
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<td>Sandover Highway</td>
<td>3</td>
<td>1286</td>
<td>73</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Plenty Highway</td>
<td>4</td>
<td>1132</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Arltunga/Amoonguna/Ltyentye Apurte/Titijkala/Aputula/Kulgera</td>
<td>6</td>
<td>1048</td>
<td>45</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Erldunda/Kaltukatjara</td>
<td>4</td>
<td>1382</td>
<td>68</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Ntaria/H.Bluff/Areyonga/Wallace Rockhole</td>
<td>4</td>
<td>645</td>
<td>38</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Papunya - Walungurru</td>
<td>3</td>
<td>1070</td>
<td>20</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Yuendumu/Nyrripi/Yuelamu</td>
<td>5</td>
<td>1168</td>
<td>53</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nganampa</td>
<td>6</td>
<td>flights</td>
<td>133</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

* round trip by road from nearest urban centre.

**4.4.2.3.2 Discussion – RAC**

There was a substantial amount of work remaining to determine whether conducting the trial in all remote communities was a realistic proposal. Each of the options was yet to be discussed in detail, as were negotiations regarding the degree of involvement of local staff. Clearly, for any option, this would be essential and those communities who refused any involvement would have been by necessity excluded from the trial.
All options however had advantages and disadvantages that deserved consideration. Importantly, all options carried a degree of risk that was difficult to estimate without prior piloting of procedures. It is highly likely that all would have been affected by events within communities. Cultural events, funerals, ceremonies and seasonal movement would have affected community consultation, utilisation of community facilities and locating children. Many communities would have had several other programs running concurrently, and some would not see this research proposal as a priority. The outcome would have been reduced recruitment, missed vaccination, protocol deviations and a delay in the time period in which the study could be completed and results obtained.

Option four may have been the only feasible method given it was a balance between the need to minimise the workload of existing staff and achieve timeliness and completeness of vaccination schedules during the trial. Mobile teams would still have been required for any option to provide support, training, monitoring and assistance with delivering vaccines, hence it was the most expensive.

4.4.3 Tracking of children

Possibly the most complex aspect of this study would have been tracking children throughout study areas. This would have been particularly problematic in remote areas, although discussions with some remote staff suggested families with infants were less likely to be mobile than adults or older children. Similarly mobility is generally confined to either connected communities (e.g. Walungurru residents tend to move between Amunturrungu, Papunya or Kaltukatjara) or to and from urban centres.

This issue was addressed in the Navajo study sites by a coordinated and comprehensive tracking system. Children were given unique IDs, which reflected the place they were initially enrolled. Recruitment logs of all children enrolled in the study were kept at every study site, which were updated fortnightly by central recruitment monitors. If a child turned up at a different site and staff queried their immunisation status or participation in the study, the recruitment log was referenced and the initial site was contacted. All sites maintained separate filing systems for local and visiting children.

A similar system could have been implemented in the Northern Territory, with staff employed at head office specifically for maintaining updated recruitment logs, and acting as a contact point for clinics or teams who have queries regarding a child’s location and/or study status. As teams would have been required to travel through several related communities each trip, the logs could have been checked in each community.

Similarly, the plan was to engage local people in every community to act as liaison personnel, specifically to assist with keeping study teams up to date with a child’s location.

However, children would inevitably be missed and therefore the support of local staff would have been essential to ensure children completed their schedule.

4.4.4 Elimination criteria

The following elimination criteria applied and would have been checked at each visit subsequent to the first visit. If any became applicable during the study, the subject would not necessarily have been required to discontinue the study, but may have been eliminated from analysis.

These criteria are:

- the development of an absolute contraindication to any of the routinely scheduled childhood vaccines, as described in the current (seventh) edition of *The Australian Immunisation Handbook*; and

- departure, or planned departure, from the Northern Territory prior to completion of the primary course of immunisations with study vaccine (i.e. within 4 months of the first dose of vaccine for those aged ≤6 months, or within 2 months of the first dose for those aged 7 months to 5 years).
Additional criteria that would have been checked for the specified categories of subjects are outlined in the scientific protocol. Some criteria would apply to all the subjects enrolled into the study; others would only apply as elimination criteria to subjects presenting with OM. If any became applicable during the study, the subject should not have discontinued the study follow-up but may have been eliminated from some analyses.

4.5 Vaccine Supply

Vaccine accountability processes are essential to maintain the quality and integrity of the study vaccine. Investigators must be confident that if a vaccinated child develops disease, it was not due to vaccine failure resulting from poor storage and/or delivery. Similarly, all vaccines supplied by the sponsor must be accounted for, not used for purposes other than those specified in the protocol, and any unused supplies returned.

SB would supply sufficient doses of the vaccine to administer up to four doses to all subjects as described in the protocol. An additional five percent will be supplied for replacement in case of breakage or inadequate storage conditions. Vaccines would be packed in labelled boxes, with labels containing the following information: study number, vaccine number, lot number and instructions for vaccine administration.

4.5.1 Methods

To assess current vaccine supply processes, discussions were held with the immunisation coordinators of Territory Health Services and the Divisions of General Practice, as well as the senior pharmacists at each of the five THS hospitals. In addition, an audit of immunisation and cold chain resources was conducted in collaboration with the Centre for Disease Control and the Top End Division of General Practice. A questionnaire was mailed to all community clinics in the NT. A random sample of clinics (n = 15) across the NT, and all GP immunisers in Darwin (n = 14), were selected for electronic temperature monitoring of vaccines during transport, and 10 subsequent days of storage in the clinic refrigerator using Hastings Data Loggers.

4.5.2 Results

The response rate to the mailed survey was 68 per cent.

4.5.2.1 Training in cold chain management

The Centre for Disease Control, THS, has developed guidelines for the ordering, storage and monitoring of vaccines in the NT. In addition, it is recommended, although not mandatory, that all staff responsible for the care of vaccines and immunising children complete an accredited course, “About giving vaccines”. This course is a combination of self-directed and competency based learning and is coordinated by Staff Development Services of THS at a cost of $50 per person. Fifty percent of services indicated they had staff performing immunisations who had not undertaken the course; of these 64 per cent had at least two or more staff who required training. One service indicated no training was necessary, as doctors were responsible for immunisations.

4.5.2.2 Distribution

Childhood vaccines are currently delivered from interstate suppliers by air on a daily basis and distributed free of charge to health services from central pharmacies at each of the five THS hospitals. Health services order directly from THS pharmacies and supplies are distributed by a combination of air (32 per cent) or road couriers (18 per cent) or direct collection by clinic staff (34 per cent). Sixteen percent of providers use a combination of methods. Eleven commercial courier services were identified.

Vaccines are generally packed in bundles of 30 with one freeze and one heat monitor per bundle. Eighty nine percent of services stated that cold chain monitors always accompanied vaccines. Of the remainder, monitors were in place most of the time. Clinics are charged a deposit for the eskies ($2.00) and for the cold-chain monitors that accompany the vaccines ($2.50 and $3.75 each). They are transported in eskies with ice bricks. There are no other fees associated with the storage and/or delivery of vaccines.
4.5.2.3 Storage

Vaccines are stored in large commercial refrigerators at each hospital, all of which are set to alarm at the hospital switchboard if temperatures rise or fall outside the acceptable 2-8°C range. Two pharmacies also record temperatures daily on temperature charts.

All pharmacies indicated they would be prepared to store and distribute the trial vaccine depending on the amount of paperwork required, the volume of vaccines at any one point in time, and appropriate reimbursement for services provided.

Ninety one percent of health services stated they had dedicated vaccine fridges in their clinics, however 43 per cent indicated there was not enough room in the fridges for additional vaccines. Sixty-six percent stated the clinic had one person who was solely responsible for cold chain monitoring. All clinics had fridge thermometers, 80 per cent of which were digital. Ninety three percent checked fridge temperatures daily, although heat/ freeze monitors attached to vaccines were checked less frequently (30.4 per cent performed daily checks, 45 per cent weekly and 23 per cent as vaccines were used).

By the end of the September, data loggers had been placed in eight clinic and 12 GP refrigerators. All were maintaining temperatures between 2 - 8°C. Temperatures during transport however were consistently higher with a range of between 10 - 15°C. These ranges are acceptable for short periods, however a review of packing for transport is required.

4.5.3 Discussion

Ensuring the integrity of the cold chain and vaccine accountability across more than 120 sites in the NT would have been problematic. While trial staff in urban centres would have been responsible for the study vaccines at their sites, quality control in remote areas would have presented several difficulties. The least of these would be space for storing the vaccine given over 40 per cent of clinics indicated they did not have enough room. Similarly approximately half the clinicians performing immunisations in the clinics had not undertaken recommended training in vaccine delivery and cold-chain management.

The most feasible means of ensuring quality control was for small amounts of vaccine to be stored at any one time, with the mobile teams replenishing stocks every 8 weeks and assessing cold-chain management. All staff directly involved in immunising children in the trial would also have been required to complete the recommended course, the cost of which would have been borne by the trial. Several centres would possibly have required new refrigerators. Data loggers would have to have been placed in all centres, with at least monthly data review.

4.6 Data management

4.6.1 Case Report Forms (CRFs)

CRFs were to be supplied by SB for the recording of all data. These consist of an original plus two carbon copies. The top copy (original) was to be transferred to the SB data management facility in India, one copy retained at the study site (either with clinic records, or in a specific study filing system) and one sent to the study monitors at SB in Melbourne. Given the vast number of sites proposed initially, it became clear that having the CRF in multiple sites would have been problematic, primarily due to the mobility of children between areas. It was therefore proposed that remote sites utilised workbooks, which were then transcribed into CRFs at head office. This would ensure that a complete CRF was maintained for each child in the study.

When a subject completed a visit, it was generally anticipated that relevant sections of the CRF are completed by the investigator (or designated staff) within 24 hours of the last data becoming available, but in no case later than five days. The same criteria apply when a subject completed a study.
Original (top copy) CRFs or log sheets must be submitted to SB for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study. This copy does not contain personal identifying information, but may contain community names and Indigenous status. The implications of the latter require consideration in greater detail, particularly with respect to intellectual property, which is discussed later. If problematic, it may be possible for these data to be excluded from the CRF and held only by the investigators.

CRFs are reviewed by a SB professional monitor at study sites. Errors detected by subsequent in-house CRF review necessitate clarification or correction of errors and documentation and approval by the investigator. Investigators are required to assist in clarification or correction of errors detected after study finalisation within 48 hours of their being brought to their attention.

4.6.2 Data entry and analysis

A requirement of SB is that they perform their own in-house data entry and analysis. This is primarily due to the degree of control of data that is required for regulatory and product development purposes. Top copies of the CRF, which do not contain personal identifying information, would be forwarded as above to Melbourne; they are then transferred overseas. The data could be transferred back to the study team electronically if local analysis is desired. One advantage of this approach is that it limits the need for the development of local databases and minimises data entry support needs. The primary disadvantages are those relating to intellectual property.

This issue of data ownership and transfer of information would need to be discussed with communities, particularly in light of ethical guidelines relating to research with Indigenous communities, and legal agreements such as those that exist between the Tiwi Health Board and MSHR.

4.6.3 Data queries

Data queries could arise both locally or from overseas. These are when errors or inconsistencies are detected and must be rectified by referral to source data. To minimise the amount of queries that arise, a large component of staff training will need to focus on data quality and recording processes.

It would be the investigator’s responsibility to ensure that data queries are addressed in a timely manner, and that procedures for correcting errors are strictly adhered to. Data queries will impact on local clinic staff, particularly as source data (ie. clinic notes) will need to be accessed and checked to verify data.

4.6.4 Archiving of Data

The study team would be required to maintain all study documentation (including SB-specific documentation) until at least two years after the last approval of a marketing application, and until there are no pending or contemplated marketing applications, or at least two years have elapsed since the formal discontinuation of the clinical development of the study vaccine. However these documents must be retained for a longer period if required by the applicable regulatory requirements or by an agreement with SB.

It is the responsibility of SB to inform the investigator/institution as to when these documents and study related records no longer need to be retained. The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

4.6.5 Discussion

Data management processes were not finalised. The study team would need to work closely with SB in the development of appropriate databases and data management systems. Possibly the most significant issue is the expectation that data will be entered and analysed external to the research team. The CRCATH would have needed to clarify this aspect of the study with SB prior to study start.
4.7 Outcome assessment

Several endpoints were proposed for the initial trial. The primary endpoint was, for most of the feasibility study, IPD. Secondary endpoints included: middle ear disease (otitis media, tympanic membrane perforation and carriage); acute respiratory infections in community settings; antibiotic use in community settings; radiologically obvious pneumonia in hospitalised children; immunogenicity; serious and other adverse events; and reactogenicity.

IPD and community based respiratory illness were excluded due to downsizing of the study, and concerns regarding the validity and reliability of historical data on respiratory illness at the community level. The information that was gathered on all proposed endpoints is however still included in this report as a reference for future work.

4.7.1 Method/Results/Discussion

4.7.1.1 Invasive Pneumococcal Disease

The primary endpoint for the NT effectiveness trial was IPD, with historical controls used as the comparison group. IPD data have been collected formally in the NT since 1995, and a formal evaluation of the system has recently commenced. This section presents a brief overview of the current system and the feasibility of utilising the system during the trial.

4.7.1.1.1 IPD surveillance in the NT

Invasive Pneumococcal Disease has been notifiable in the NT under public health legislation since January 1995. It is a passive, laboratory based notification system using the following case definitions:

- *S. pneumoniae* isolated from blood, CSF or other normally sterile site; or
- detection of gram positive diplococci on microscopy if not cultured from a sterile site (generally reported as gram positive diplococci resembling streptococcus); or
- a clinically compatible illness and detection of antigen from a clinical specimen (eg. urine).

The majority of notifications are received from THS hospital laboratories; rarely from private laboratories. Since 1995, all serotyping of isolates has been performed at Queensland Health Scientific Services (QHSS) in Brisbane (Figure 2), with the exception of isolates from Western’s Pathology which are processed at PathCentre Perth (notifications are rarely received from these laboratories). QHSS does not charge for serotyping as it is considered a public health service. QHSS reports either directly to CDC Darwin or to the AHS laboratory which then forwards data to Darwin.

Delays in reporting of serotypes are minimal. There are however delays in isolates from Central Australia reaching QHSS as ASH laboratory transports in batches, because of the high cost of transporting infectious materials. The completeness of serotype data for the period 1994 - 1998 is 85 per cent.
Notifications throughout the NT are followed up using a standard form developed by CDC. This consists almost entirely of medical record review; a patient is usually only contacted if they are an inpatient at the time of notification, and prior vaccination status needs determining. The format of follow-up has not altered since the system’s inception. Data are forwarded from each of the regional Centres for Disease Control on a paper-based system to head office in Darwin where they are entered into an EpiInfo v6 database. One person in Darwin has had responsibility IPD surveillance since 1995 during which time there have been no alterations made to the system.

There are currently no planned changes, however an anticipated review of IPD surveillance at the national level (Vicki Krause, CDC, personal communication) may precipitate changes in process and/or format in the near future. For the trial to access these data, a formal agreement with CDC would have been required for release of the information to the trial team. Individual consent at the time of recruitment would also have required permission for release of these data to the researchers.

Assessment of IPD outcomes would need to account for any changes in existing practice, particularly with regard to the taking of blood cultures. There is potential for clinical practice to alter in the presence of a vaccine, i.e. clinicians may be more or less likely to take blood cultures. The current indications for the collection of clinical specimens are outlined in Box 1. It will be important to monitor any changes in the total numbers of cultures taken over time throughout the life of the trial. These data may have been available through the two major laboratories, RDH and ASH.
Box 1: Current indications for collection of clinical specimens

<table>
<thead>
<tr>
<th>Blood Cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unlikely to be done in many bush communities due to difficulty of procedure. Would be dependant on skill base of clinic staff and/or resident MO and facilities available</td>
</tr>
<tr>
<td>• Hospitalised children – all with fever $\geq 38.5^\circ$C should have cultures performed.</td>
</tr>
<tr>
<td>• The two standard treatment protocols in the NT recommend the following:</td>
</tr>
<tr>
<td>a) CARPA – only suggested for suspected meningitis and osteomyelitis</td>
</tr>
<tr>
<td>b) Children’s Standard Treatment Manual – recommended for septic arthritis, osteomyelitis, transient synovitis, and meningitis.</td>
</tr>
<tr>
<td>• Both manuals recommend cultures be taken before antibiotics are given but treatment should not be delayed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Likely to occur only in hospitalised children</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Joint Aspirates</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recommended in both treatment manuals when clinically indicated and should be done before antibiotics are given.</td>
</tr>
</tbody>
</table>

4.7.1.2 Radiologically Obvious Pneumonia (ROP) in hospitalised children

The efficacy of the study vaccine in preventing hospitalised radiologically confirmed pneumonia is difficult to predict from studies of existing vaccines. There were several reasons for assuming significant differences in this population, including:

- a large proportion of Aboriginal children who have chest radiographs (CXRs) do not have “typical” acute pneumonia;
- the propensity for most cases of pneumonia in the community to be treated with intramuscular penicillin and without radiography; and
- most children who have been evacuated to hospital with respiratory illness have other comorbidities requiring treatment.

Pneumonia would be defined in accordance with criteria proposed by the World Health Organisation Conjugate Pneumococcal Vaccine Trialists Group. A case of primary-endpoint pneumonia is defined as the presence of alveolar consolidation and/or pleural fluid on plain CXR in a child with a clinical illness consistent with acute lower respiratory tract infection. These diagnostic criteria would be standardised by the Trialists Group prior to the study.

A single paediatrician and a single radiologist, who had been involved in standardisation and calibration processes, would read the CXRs. Any films on which the paediatrician and radiologist disagreed would be sent to the WHO radiologists reference panel for final reading. The reference panel would categorise these films as positive, negative, or uncertain; uncertain films will be considered negative for the endpoint analysis. Ongoing quality maintenance of radiograph reading will be ensured by review of a subset of all agreed positive and agreed negative films by the WHO reference panel, to ensure that the criteria being used by each vaccine trial and each site are consistent with each other. Should the NT readings be considered at odds with those from other trials and other sites, the paediatrician and radiologist will seek advice from the Trialists Group about retraining or restandardisation.
A paediatrician and radiologist would examine all CXRs taken for possible respiratory disease on hospitalised Aboriginal children aged 2-23 months for two 12-months periods: January 1 to December 31 1999 and January 1 to December 31 2000. The incidence of primary endpoint pneumonia will be compared for the two 12-month periods to ensure that the rate does not vary substantially from year to year. Chest radiographs will continue to be read until the date of first vaccination with study vaccine.

The baseline incidence rate will be that for the 12-month period immediately preceding the first vaccination. All CXRs taken for the same indications will be read in the same manner for the period ending 12-months after the date of first vaccination, and again for the ensuing 12-month period. The before and after incidence rates will be compared to determine if there has been a significant reduction in incidence of hospitalised endpoint radiological pneumonia coinciding with the introduction of study vaccine.

4.7.1.2.1 Methods - ROP

To assess the feasibility of measuring this outcome, we examined several aspects of the proposal including:

- the locations in which radiography facilities exist;
- radiology information systems, and the ability to digitalise films;
- ease of access to historical films;
- the current indications for CXRs in children under two years of age; and
- determining the number of CXRs taken per year in the target group by diagnosis and reason for CXR.

Discussions were held with senior staff in each of the departments and, for examining indications for CXR, with senior paediatricians. Standard treatment manuals were reviewed.

4.7.1.2.2 Results - ROP

Current services

Radiology departments are located in each of the five THS hospitals, Darwin Private Hospital and in three remote communities in the Top End. Public services are contracted by THS to NT Imaging in the Top End and to Jones & Partners in Central Australia.

Films from the three regional centres are referred to either Darwin or Alice Springs for reporting. From July 2000 neither of these centres had permanent full time radiologists attached to the departments. The private contractors provide locum staff from Adelaide on a 2 - 4 week rotational basis.

Radiography facilities are located at Jabiru, Nguiu and Maningrida. Films are taken either by visiting radiographers or the resident medical officers if they have been trained. Procedures are rarely performed on infants. NT Imaging is contracted for reporting.

Information Systems and Digitalisation Facilities

All THS centres have radiology information systems linked with CARESYS (the NT public hospitals patient administration system). Data collected is limited to client demographics, procedure type, requesting medical officer, inpatient/outpatient status, public or private status and time. There is a field that states the reason for the procedure however this information cannot be extracted locally. There are standardised reporting functions, which do not allow local manipulation of data. More specific reporting requests are referred to the Business Information Management Unit (BIM) of THS. A new information system is currently being developed which may be online within 2001.

No THS sites have digitalisation facilities. Copies of films can be made by the radiographers at a charge of $5 per copy. They would not be able to cope with large volumes of requests without additional support.
NT Imaging practices use a separate information system in their private facilities. The data collected are limited to client demographics and occasions of service information, with limited reporting and manipulation abilities. They have digitalisation facilities with tele-radiography links between sites and head office in South Australia. The facility is not available for public services.

Access to films

Historical films will be available at all THS sites but the research team would need to provide staff to access the films and ensure they are tracked appropriately on CARESYS.

Private films taken at NT Imaging facilities are returned to the patient, although some GPs may store films at their practices. As a result, accessing these films may be a substantial problem. There may be access to films that have been digitalised, however the images are not stored for greater than a few months and are destroyed regularly. While the company has supported research in the past, and would be likely to support this one, the impact on their resources for accessing films, data and equipment will need to be considered by company executives.

As consent will not have been obtained from individuals permitting access to historical films, all custodians and the regional ethics committees will need to approve access to data and films on their behalf. Indications for CXR in children under two years of age

Discharge diagnoses and coding of episodes in which a chest film has been taken should be reasonably consistent, however if greater specificity is required then it may be necessary to exclude codes relative to bronchiolitis. Excluding those with a diagnosis of viral pneumonia and asthma may be problematic. It was suggested that all separations for Aboriginal children with a diagnosis of diarrhoea, malnutrition and/or dehydration should be included.

Frequency of CXRs in the target population

Data were obtained from the BIM unit of THS to determine the number of procedures each year in eligible children, the frequency of relevant DRGs and consistency over time. Reliable data are not available for earlier than 1997 and Outpatients Department data have not been validated. Table 2 provides a breakdown of the number of CXRs performed for respiratory and non-respiratory indications for the period 1997 - 1999 by rural/urban and Indigenous/non-Indigenous status.

Table 4: Number of Chest Radiographs performed in THS facilities by rural/urban, Indigenous/non-Indigenous and clinical indication, 1997-1999 (excludes 144 episodes with unknown Indigenous status).

| Year | Rural | | | | | Urban | | | |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
|      | A - R | A - nR | O - R | O - nR | Subtotal | A - R | A - nR | O - R | O - nR | Subtotal | Total |
| 1997 | 363    | 157    | 42    | 35    | 597      | 52    | 29    | 104   | 81    | 266      | 863   |
| 1998 | 654    | 172    | 90    | 23    | 939      | 150   | 65    | 396   | 99    | 710      | 1649  |
| 1999 | 736    | 221    | 90    | 36    | 1083     | 141   | 46    | 412   | 124   | 723      | 1806  |
| Total| 1753   | 550    | 222   | 94    | 2619     | 343   | 140   | 912   | 304   | 1699     | 4318  |

A - Aboriginal and/or Torres Strait Islander

O - Other

R - respiratory related DRG

nR - non respiratory related DRG
There appears to be a large discrepancy in CXRs in the dataset between Central Australia and the Top End. From 1997 - 1999, 97.6 per cent of episodes pertained to residents of the Darwin, Katherine or East Arnhem regions, 0.1 per cent for those from either the Barkly or Alice Springs regions, and district was missing for 2.3 per cent (THS, unpublished data). Discussions with the radiology department at Alice Springs has to date failed to determine the cause of the discrepancy, however a manual check of CARESYS reports in the department revealed at least five CXRs had been taken on infants in the preceding week alone. An inability to rely on information systems in the department would be a significant impediment to successfully measuring this endpoint unless this system could be improved.

4.7.1.2.3 Discussion - ROP

Organisationally, access to and review of CXRs would not have been problematic (provided database issues in ASH were resolved). The two major radiology facilities in the NT did not raise any objections, conditional upon approval from the appropriate ethics committees and the private contractors’ management interstate. Given current staffing issues, a part-time project officer would need to be employed for a short period each year to collect, copy and forward films to the nominated reviewers.

There were however several unresolved methodological issues. The analysis would have needed to adjust for any changes in the referral pattern of children to hospital and any concurrent changes in the incidence of respiratory illness in Aboriginal communities. The former could have been estimated using data on evacuations from remote Aboriginal communities of children with non-respiratory illnesses. This would have been estimated during the secondary endpoint studies of the incidence of clinical pneumonia in Aboriginal communities. These would have provided an estimate of the change in incidence of lower ARI and of antibiotic use in a subset of communities – any changes could be extrapolated to the whole region.

Separate analyses would have been needed for children resident in Alice Springs with a diagnosis of possible or probable pneumonia. Urban children are more likely to have a chest radiograph performed for acute LRI simply because of easier access to services.

4.7.1.3 Otitis Media And Bacterial Carriage

4.7.1.3.1 Background

Otitis media is an infection or inflammation of the middle ear and is a common childhood illness. The hearing loss associated with otitis media causes delays in development of auditory processing and language development and is a disadvantage educationally and socially. *Streptococcus pneumoniae* causes the majority of otitis media episodes and is believed to be associated with greater severity of symptoms. Non-typeable (or non-encapsulated) *Haemophilus influenzae* (NTHi) is the second most common bacterial cause of otitis media and *Moraxella catarrhalis* is associated with approximately 15 per cent of cases.27

Combined infections, which are common among Aboriginal children, are rare in developed countries. The presence of a combined infection dramatically increases the probability of early onset and severe otitis media and reduces the likelihood of natural cure.

Data on Northern Territory Aboriginal infants show that ear effusions do not resolve without treatment and can evolve into chronic suppurative otitis media (CSOM, discharge through a perforated ear drum for 6 weeks or more).24 Several NT studies have shown that up to one-third of Aboriginal children have acute perforations by six months of age and that up to two-thirds of these infants have acute perforations or CSOM by the age of 12 months.23;4;9;10 It should be noted that in 1996 the World Health Organisation recommended that an eardrum perforation prevalence in excess of four percent should be considered a massive public health problem requiring urgent attention.

The extent of the problem is further illustrated when one considers that fifty percent of school aged Aboriginal children in one community were found to have middle ear disease (otitis media) and associated hearing loss requiring use of hearing aids (THS Hearing Services, unpublished data).
This contributes to poor school achievement. It is very clear that it will be difficult to achieve higher standards of education while children have the degree of hearing loss that currently exists.

A major benefit of the conjugate pneumococcal vaccine may be in preventing many episodes of otitis media. If pneumococcal vaccine serotypes cause 40 per cent of OM episodes and if the vaccine is 60 per cent efficacious, a 24 per cent reduction in acute otitis media may be expected. The public health benefit of such a reduction in the incidence of otitis media is likely to be huge, especially for Aboriginal children.

In addition, the conjugate vaccine carrier protein is a conserved outer membrane protein of *H. influenzae*. Whilst this protein is not yet known to have any clinical benefit, it is plausible that some protection from infection will occur. Animal model studies showing increased clearance of *H. influenzae* from the lungs and ears, support this suggestion.28

### 4.7.1.3.2 Aim

To ascertain the level of community support, and the research capacity for including otitis media and upper respiratory carriage outcomes within the main project. It was expected that the Otitis Media and Respiratory Carriage Project would be carried out in a subset of the main trial population.

### 4.7.1.3.3 Methods

- Liaise with health care providers in the NT and members of the Tiwi Health Board to ascertain support for the sub-project.
- Include information on otitis media in the consultation process (include in slide presentation and information kit) and collate any specific feedback on the subject.
- Liaise with the design and logistics team for the purpose of developing:
  - scientific protocol;
  - implementation plans; and
  - budget.

### 4.7.1.3.4 Results

**Bathurst Island**

The main reasons behind considering Bathurst Island for the Otitis Media project were:

- the well established infrastructure with processes for assessing research proposals (Tiwi Health Board);
- the availability of data on ear disease and respiratory carriage in the Tiwi people;
- the area’s demonstrated interest in and support of otitis media research; and
- indirect support from the Tiwi Health Board (THB) regarding vaccination interventions.

**Central Australia**

The proposed study had been geographically confined and included Central Australia. Reasons for this decision will be discussed in the main trial summary. The Feasibility Study team is not aware of any data on otitis media which is specific to Central Australia.
Consultation

Consultation to date has revealed interest in the concept of the otitis media project. The consultation process in Central Australia included only four communities and was delayed until after a decision by the CRCATH on whether or not to proceed with the proposed effectiveness trial. It should be noted that at the time of consultation with some members of the Tiwi Health Board, the trial had not been geographically confined to Central Australia and Bathurst Island, and the availability of Prevenar™ had not been investigated, or reported, in detail. A preliminary letter to the Tiwi Health Board seeking an expression of interest in participation in the trial, despite the possibility of the licensed vaccine, Prevenar™, being available in 2001, received a very positive response.

Logistics and Design

After much consideration and debate it is expected that the project would involve visits at eight weekly intervals to assess nasal [nasopharyngeal] carriage rates in children on Bathurst Island only. Ears would be examined for perforation cross-sectionally three times over a 2-year period in both geographic areas in children aged 6-15 months. A subgroup of 91 children would need to be recruited as per the draft protocol.

4.7.1.3.5 Discussion

Resolved Issues

- The THB are aware of the proposed trial through informal discussions with Dr Amanda Leach (Microbiologist, Ear Health and Education Unit) and through the dissemination to the THB of minutes of a meeting where the project was discussed.
- Preliminary Discussions were held with the Clinical Director, Educator, and Policy Development Officer in April 2000. Each was supportive of the concept of the initial proposal.
- The interest in otitis media is evidenced by previous participation in ear health projects, which have been initiated by The Menzies School of Health Research over the past 10 years.
- The Ear Health and Education Unit have three studies on Bathurst Island which are ongoing; one is in draft report stage. It is planned that each of these projects will have completed their clinical phase by 2001.
- The Ear Health and Education Unit have funding for a Tiwi project on Chronic Suppurative Otitis Media (CSOM) to commence in late 2000 and run throughout 2001. It is not thought that this project would conflict with the recruitment for the proposed trial as the inclusion criteria will most likely confine the trial to children over the age of two years.

Unresolved Issues

- Detailed discussions had not been held with any communities on ear disease endpoints
- Due to the changes in the direction of the main trial all people that were consulted or contacted were subsequently updated.
- The scientific protocol requires refinement before budget and logistics can be finalised.

4.7.1.3.6 Recommendation

Based on the limited consultation to date, and the interest demonstrated by the people of Bathurst Island (as indicated by their history of involvement in research in ear disease), it was recommended that the possibility of conducting a trial in otitis media, in a subgroup of the main trial population, be further explored.
4.7.1.4 Respiratory Illness and Antibiotic Use in the Community

These end-points were considered to assess the effectiveness of the SB vaccine in preventing presentations with a clinical diagnosis of acute lower respiratory tract infections in Indigenous children, and in reducing the number of courses of antibiotics administered for both respiratory infections and all other causes.

**Respiratory illness**

The case definition was planned to be that used in the Central Australian Rural Practitioners Association (CARPA) Manual:

**Pneumonia:** A child with a cough or fast breathing, with a respiratory rate of 50 per min or more (aged 3 months to < 1 yr) or 40 per min or more (aged 1 yr to < 5 yrs).

If possible, fever will be added to this definition. Children aged <5yrs (or <2yrs should catch-up only take place up to age 2yrs) who present with a clinical diagnosis of pneumonia would be recorded prospectively by community health staff. Any presentation with the same diagnosis within two weeks of a previous diagnosis would not be considered a new episode. Other respiratory presentations with a diagnosis of acute respiratory infection, not pneumonia, would also be recorded.

At least six months of baseline data would be required depending on further examination of issues such as stability of data over time and seasonal effects (if any). The analysis would have compared the incidence of presentations of clinical pneumonia before and after vaccination after 12 months, and again after 24 months. A further analysis would have compared the incidence of all clinical acute respiratory infections before and after vaccination.

**Use of antibiotics**

At baseline and at the completion of 12 and then 24 months, the use of antibiotics in children aged <2yrs (or <5yrs) would be calculated as follows:

- Courses of antibiotics (oral and intramuscular) for all indications
- Courses of antibiotics (oral and intramuscular) for respiratory infections

The most appropriate method for collection of these data would be determined in consultation with health staff in the communities involved.

4.7.1.4.1 Results

To our knowledge, there are limited sites in the NT that have systematic recording of clinic presentations, particularly those that record diagnoses or reasons for presentation in detail.

These sites include clinics participating in the Coordinated Care Trials, Yuendumu, Yuelamu, Nyirrpi and Nganampa Health Service. The latter appears to have the longest period of collection.

Accurate recording and coding of data appears to be dependent on the skills of the staff who review the child, and enter the data. An audit of the system in some Central Australian communities revealed discrepancies between clinic notes and the surveillance system of between 13 - 25 per cent.29

4.7.1.4.2 Discussion

Valid and reliable results for these endpoints would be primarily dependent on the quality and consistency of baseline data collection in communities. While individual health services may collect some data, standardising this process across communities to ensure comparability of data would have been a time consuming and challenging process.

If these endpoints are to be considered for any study, a review of data collection methods and an audit of data quality in participating communities will be required prior to the study starting.
4.7.1.5 Immunogenicity

4.7.1.5.1 Background

Immunogenicity assays would have been performed in a subset of study subjects (100 - 200 Aboriginal children). Only a subset is required as extensive data are being collected in other studies. Past experience with reduced immunogenicity of Haemophilus influenzae type B (Hib), Hepatitis B (Hep B) and Oral Poliomyelitis (OPV) vaccines in Australian Aboriginal children suggested it was important to specifically assess immunogenicity in this population.30-32 Because children would have been receiving concomitant vaccines, a control group for the immunogenicity assays would be required.

Priorities for the assays are antibody responses to vaccine serotype pneumococci and Protein D. These entail evaluating the immune response to the eleven pneumococcal serotypes and Protein D after dose three. A secondary objective is to evaluate the presence of any interference by the SB pneumococcal vaccine with the immune response to other vaccines administered at the same time. This is important, as this study would be the first of any of the SB pneumococcal vaccine trials around the world where the vaccine would be given concurrently with the Hib vaccine PRP-OMP (PedvaxHIB™).

To ensure enough serum was available to measure all relevant antibodies (minimum of 3mls of whole blood), and minimise the risk of haemolysis interfering with laboratory assays, venepuncture is desirable. Sera must be stored and transported in a vertical position at -20°C. SB Belgium would perform all laboratory assays.

4.7.1.5.2 Methods

Preliminary discussions only have been held with paediatricians and laboratories to determine if serum banks are available and/or the feasibility of obtaining control sera from children not enrolled in the study.

4.7.1.5.3 Results

Children would be recruited from one - two large communities, with procedures specific to this outcome included in the informed consent process. Given the difficulties in performing venepuncture on infants, further consideration would be required as to who would collect the samples.

Control groups would need to be accessed from the general population. The most feasible option would be to recruit children admitted to hospital who are having routine blood tests performed, with additional sera collected at that time. This would need to commence approximately six months prior to the first child being vaccinated to ensure sufficient samples had been taken before widespread vaccination commenced. Given that sera from vaccinated children needs to be obtained at approximately seven months of age, it may take considerable time to recruit sufficient controls in this age group. An acceptable age range for the latter needs to be determined by SB.

The proposal was discussed with paediatricians at Alice Springs Hospital who would have been willing to assist with the immunogenicity studies. Consent and sample collection could have been developed as a standard admission procedure for the target group. This would have been dependent on appropriate consent procedures, ethics clearance and the provision of a research assistant to perform the relevant tasks.

Alternatively, there were some sera available from studies conducted on the Tiwi Islands. There are approximately 80 samples, which have been stored at -70°C for up to three years from children aged 7 - 12 months. Access to these sera would be dependent on approval from the Tiwi Health Board and the Top End Ethics Committee. The usefulness of these sera was dependent on this group being deemed a valid control group.

4.7.1.5.3.1 Discussion

The major difficulties associated with the immunogenicity studies would have been the added complexity of the consent process for some children and the ability to recruit enough children in the control group in a reasonable time frame. The storage and transport of sera from remote communities may also be problematic, and portable freezers would be required.
Furthermore, the collection and storage of blood from Aboriginal people presents cultural and ethical difficulties in some areas. Body fluids are closely associated with spirituality and the prolonged storage of serum samples may not be allowed.

4.8 Adverse events

As the vaccine is an unlicensed product and will be administered within the confines of a research protocol there are additional safety reporting responsibilities. The documentation and evaluation of adverse events on an ongoing basis helps to ensure the safety of the study population as well as meeting the standards outlined by ICH Good Clinical Practice guidelines, government regulations and the sponsor company’s standard operating procedures.

An adverse event is any untoward medical occurrence, related or unrelated to the study drug, which occurs in a person who is in a trial. An adverse event will be considered serious if it falls into any of the following categories:

- results in death;
- is life-threatening;
- results in persistent or significant disability/incapacitation;
- requires in-patient hospitalisation, or prolongation of hospitalisation;
- is a congenital anomaly/birth defect in the offspring of a study subject; or
- is an important medical event that may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above.

In the Northern Territory adverse events following immunisation are also notifiable to the Centre for Disease Control (CDC) which then notifies the Adverse Events Drug Reactions Advisory Committee (ADRAC), which receives reports on unexpected and serious adverse events following immunisation across Australia.

While the study proposal has changed considerably over the past six months, the requirements for adverse event reporting have not. Hence the proposed methods for collecting safety information are the same for any study design.

4.8.1 Method

Proposals for adverse event and serious adverse event reporting were developed based on discussions with SB and direction from the CRCATH. Hospital separation data were used to estimate the number of potential SAEs related to hospitalisation.

4.8.2 Results – Non Serious Adverse Events (NSAE)

Adverse events as defined by The Australian Immunisation Handbook, 7th Edition, occurring in the study population will be reported as per the same requirements for all vaccines.

Collection of non-serious adverse events in the NT will be problematic for the following reasons:

- For the data to be useful, detail such as the duration, intensity and causality of the event will need to be collected. This would be logistically impossible to do for all children in the trial due to such issues as isolation, lack of communication facilities and staffing and budgeting constraints.
- The absence of a control arm means that the results would be subject to unknown biases.

Because of these difficulties it was agreed that the collection of NSAEs would be restricted to a sub-group of the population with a control arm in a group of children not receiving the study vaccine.
It was determined that reactogenicity data would be valuable. Reactogenicity refers to the intensity of localised and systemic symptoms that follow from vaccination. These include pain, redness and swelling at the injection site together with drowsiness, fever, irritability/fussiness and loss of appetite. Parents are usually asked to record the intensity of these reactions for up to one week post vaccination on diary cards.

However the following issues have yet to be addressed:

- the number of children required; and
- how to make the data meaningful given that reliance on diary cards may be problematic in some communities.

Interviewer administered questionnaires would need to be used and it was suggested they be administered on days 2, 7, 14, and 30 post-vaccine. These procedures would need to be developed and piloted prior to study start to ensure they are both culturally and linguistically appropriate, as well as internally valid.

4.8.2.1 Discussion – Non Serious Adverse Events

While safety monitoring for NSAEs is an ongoing responsibility it is not the primary outcome of the trial. The study is designed as a test of vaccine effectiveness. The implications for collecting data for NSAE include significant additional resources, acceptability to the Indigenous community and validity of the data collected.

NSAEs have been and are being monitored in all phase 1 and 2 and other phase 3 studies of the candidate vaccine, including a study of 4000 children in Europe. These adverse events are entered into the SB worldwide safety database and used to assess the ongoing safety of the vaccine.

4.8.2.2 Results - Serious Adverse Events

Reporting Time Frames

The total reporting period for SAEs for each child enrolled will be from administration of the first dose of study vaccine to six months following administration of dose four (booster dose).

SAE Reporting Procedures

1. Parents would be given information on SAE definitions and reporting procedures at the enrolment visit. This information would be supported by supplying contact phone numbers for SAE notification on:
   - patient identification card; and
   - a personal reminder for parents, the format of which had not been finalised.

2. Parents would be requested to contact a research staff member as soon as an SAE occurred. (24hr number/answering machine will be provided).

3. Research/clinic staff would report the notification of any SAE to the SAE coordinator immediately upon learning of the event.

4. Research staff would check with Aerial Medical Services and hospital Patient Services Departments and at least twice per week for any evacuations or admissions of children in the study age group from the communities involved in the study.

5. Parents would be asked about occurrence of SAEs prior to vaccination at visits 2 (2nd dose), 3 (3rd dose) and 4 (4th dose).

6. At visits 2 (2nd dose), 3 (3rd dose) and 4 (4th dose), the research staff would also review the patient’s medical records for SAEs and possible contraindications to vaccination prior to immunisation.

7. Every three months the list of study participants would be checked against the NT Hospital Morbidity Dataset to identify any study participants admitted to hospital who had not been identified by the procedures listed above.
8. In the event a SAE became evident at the time of the next visit, the research staff would make a decision regarding the next vaccination on the basis of current contraindications as outlined in *The Australian Immunisation Handbook 7th Edition 2000*. This should only be necessary if the Medical Officer cannot be contacted in a timely manner.

9. Mobile teams in rural areas would be required to call each clinic to solicit for SAEs within 7-14 days following vaccination.

10. Regular liaison would occur between research staff and DMOs to identify children who had been evacuated from remote communities.

11. A 24-hour telephone number, linked to an answering machine, would be provided to all remote clinic staff for notification of any event.

**General**

Notification stickers would be applied to the front of all medical records from hospital archives, CHCs, participating GPs and the remote clinic records, requesting that research staff be alerted if the child presented at the hospital for any reason.

Hospital staff would be asked to report this presentation to study staff as soon as the event occurred. District Medical Officers and the GPs not participating as study centres would be notified of the study and asked to report any SAEs to research staff.

**Notification Requirements**

The SAE Coordinators would be responsible for reporting SAEs to SB within 24 hrs of the initial notification of the SAE to research staff. The Principal Investigator would be notified of the SAE as soon as possible after notification to research staff. A medical officer would review SAEs as soon as possible after learning of the SAE, assign causality, severity and determine whether the child should be withdrawn from the trial.

The minimum information required for reporting within the 24 hour time frame is:

- patient identifiers (initials and enrolment number);
- whether study vaccine has been administered; and
- nature of the event.

In addition, notifiable vaccine-related adverse events would be reported to the Territory Health Services’ CDC in accordance with requirements stipulated in *The Australian Immunisation Handbook 7th Edition 2000*.

**Expected number of adverse events**

The expected numbers of hospital separations and deaths in the study population each year (by study option) are presented in Tables 2 & 3. These data assume recruitment rates of 70 per cent in the non-Indigenous and 80 per cent in the Indigenous populations. They provide indications of the extent of events that will be need to be reported and investigated as potentially serious adverse events.

**Table 4: Expected hospital separations per year, all causes, in the study population**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ALL NT &lt;2 yr olds</th>
<th>CA + TIWI &lt;2 yr olds</th>
<th>TIWI + NHC &lt;5 yr olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous</td>
<td>2213</td>
<td>1254</td>
<td>243</td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>2717</td>
<td>328</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>4930</td>
<td>1582</td>
<td>243</td>
</tr>
</tbody>
</table>

*Source: Business Information Management Unit & Epidemiology Branch, THS, unpublished data CA – Central Australia, NHC – Nganampa Health Council*
Table 5: Expected deaths per year, all causes, in the study population

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ALL NT &lt; 5 yr olds</th>
<th>CA + TIWI &lt; 5 yr olds</th>
<th>TIWI + NHC &lt; 5 yr olds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous</td>
<td>30</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>8</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>


Staffing

Given the workload associated with adverse event reporting and follow-up, dedicated staff would be needed to ensure safety was adequately monitored during the trial. The experiences of clinical trials elsewhere suggest the time taken for one person to respond to and follow-up adverse events is approximately one day per event. For the NT wide option, this would have translated to 13 staff working full time on adverse events alone.

4.8.2.3 Discussion – Serious Adverse Events

Concomitant administration of multiple vaccines in this trial, and the absence of a control group, means it would not have been possible to determine causal relationship of general adverse events to the individual vaccines administered. Comparing overall hospitalisation rates between vaccinated and unvaccinated children would provide some indication of potential problems. This would need to be performed regularly to ensure there was timely review of safety information throughout the trial. Assessing the safety of the SB vaccine in this population would have been complex, hence critical review of safety data from the Phase I, II and other phase III trials of the SB vaccine would be essential prior to the trial starting.

Due to the frequency of hospitalisation of NT children, there would be significant numbers of events reported in this trial which would require detailed and timely follow-up. Although the majority would be unlikely to be vaccine related, it would be difficult to differentiate as to whether they were related to the trial vaccine or to the routine schedule vaccines, or were a chance event. Monitoring would have consumed considerable human resources, therefore adding significant cost to the trial.

4.9 Staffing and Human Resource Management

Staff that would be required for the trial include:

- a full time Principal Investigator with a medical background, ideally with clinical research, paediatric, immunisation and infectious diseases experience;
- a Field Director responsible for day to day running of the trial;
- Clinical Research Assistants (CRAs) for training and quality assurance purposes;
- administrative assistants;
- Data Manager and/or Data Entry Clerk;
- Aboriginal Community Liaison Officers;
- Registered Nurses, preferably with remote area health and/or research experience;
- Aboriginal Health Workers;
- Participant Recruitment Officers; and
- Adverse Event and Outcome monitors (RNs or Senior AHWs)
Recruitment and retention of skilled staff has long been a significant issue for health services in the NT. The initial proposal for a NT wide study produced a staff quota of greater than 50 people. Cost issues aside, the recruitment of sufficient qualified staff, training them in clinical research, cross cultural issues, bush survival skills and providing orientation to the NT was clearly going to be problematic, particularly given the need to commence the study early in 2001.

Similarly, retaining staff would be challenging. Clinical research tasks can be demanding and repetitive, and personnel need to be committed to the outcomes. Wages and conditions would need to be attractive and consistent with routine staff performing similar tasks, particularly remote area nurses.

### 4.10 Study Management

The administering institution for the study would be MSHR. Organisationally, SB and the CRCATH (Figure 3) would co-jointly oversee the trial.

![Organisational Chart](image)

The quality processes required in the conduct of clinical trials are defined as “Good Clinical Practice” (GCP). They are minimum standards, formalised in 1996, which have been developed by regulatory authorities and industry representatives from around the world. Clinical trials must be performed in accordance with these guidelines or the sponsor and/or regulatory bodies may consider them unacceptable.

### 4.11 Protocol Amendments and Modifications

No changes to the study protocol would be allowed unless discussed in detail with the SB’s Clinical Project Manager and filed as an amendment/modification to the protocol. The exception would be those changes necessary for the immediate care and safety of participants.

Any amendment/modification to the protocol would be adhered to by the participating centre(s) and would apply to all subjects. Written ethics committee approval of protocol amendments will be obtained prior to implementation; modifications will be submitted to ethics committees for information only. Changes to protocol would also require new consent forms to be signed.
4.12 Termination of Study

Endpoint collection would cease when the last child enrolled reached two years of age. Both the CRCATH and SB independently reserved the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification would be tendered by either party.

4.13 Monitoring by SB

Monitoring visits by a professional representative of the sponsor would be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject has completed. It is anticipated that monitoring visits would occur at a minimum frequency of once every eight weeks.

These visits are for the purpose of confirming that SB sponsored studies are being conducted in compliance with the relevant Good Clinical Practice regulations/guidelines, verifying adherence to the protocol and the completeness and exactness of data entered on the CRF and Remote Data Entry (RDE) screens and Vaccine Inventory Forms. The monitor would verify CRF/RDE entries by comparing them with the source data/documents that would be made available by the investigator for this purpose. Data to be recorded directly into the CRF/RDE screens would be specified in the source documentation agreement form that is contained in both the monitor’s and investigator’s study file. In cases of RDE, the monitor would mark completed and approved screens at each visit. At the end of the monitoring visit, the monitor would transmit the electronic data. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits.

4.14 Auditing

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for SB or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, there is agreement to permit Drug Regulatory Agency and SB audits, providing direct access to source data/documents. Furthermore, if an investigator refuses an inspection, the data may not be accepted in support of a New Drug Registration and/or Application.

Having the highest quality data and studies are essential aspects of vaccine development. SB has a Regulatory Compliance Group who audit investigation sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SB sponsored studies are in accordance with Good Clinical Practice guidelines and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigation sites to audit. These audits usually take one to two days. The SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on vaccine accountability. The SB audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SB of the validity of the database across investigation sites.

The Inspector will be interested in the following items:

- log of visits from the sponsor's representatives;
- IRB/HREC approval;
- vaccine accountability;
- approved study protocol and amendments;
- informed consent of the subjects (written or witnessed oral consent);
- medical records supportive of CRF data;
- reports to the IRB/IEC and the sponsor; and
- record retention.
To accomplish the above functions, it will be essential that the consent process includes informing participants and their communities that regulatory authorities and/or the sponsor will require access to their medical records. These inspections would always be conducted in the presence of the investigator and/or site manager.

4.15 Intellectual Property

4.15.1 SB Requirements

SB requires that all information communicated by the company remains the exclusive property of SB, and that the researchers ensure the same shall be kept strictly confidential by any person connected with the work. They ask that any information shall not be disclosed, either orally or in written form, to any third party without their prior written consent. We are required to communicate the results of the work promptly to SB.

SB agrees that the researchers have the right to publish or permit the publication of any information or material relating to or arising out of the work after prior submission to the company, provided that, if requested, publication is delayed for a maximum of six months to enable SB to protect its rights in such information or material. Any proposed publication or presentation (e.g. manuscript, abstract or poster) for submission to a journal or scientific meeting, should be sent to the SB Site Monitor prior to submission, together with confirmation that any other author(s) has seen and agreed to the proposed publication/presentation. SB will undertake to comment on such documents within four weeks.

All rights and interests world-wide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of the study protocol or which otherwise arise from the information or materials supplied under agreements reached with the company, shall be assigned to, vest in and remain the property of SB.

4.15.2 CRCATH Requirements

The CRCATH normally assumes full intellectual property rights for CRCATH projects. The CRCATH wants to ensure that there are no restrictions on analysis and publication of results of this project. The CRCATH is prepared to negotiate reasonable consultation and consideration of the views of partner organisations. Since the CRCATH is not an incorporated body, the CRCATH core partners would assume collective ownership of intellectual property arising from this project.

The CRCATH supports the approach to research in the Tiwi Islands as outlined in the agreement between the Tiwi Health Board and the Menzies School of Health Research. This agreement has served to enhance and develop research activity and improve relationships between researchers and the Tiwi people. To date the Tiwi Health Board has not canceled any research projects operating under the terms of this agreement.

If the trial proceeded on the Tiwi Islands the CRCATH expected that it would be conducted under the terms of this agreement, whether the trial is managed by the Menzies School of Health Research as the CRCATH Agent or by one of the other CRCATH core partners.

The feasibility study team has not identified similar agreements with other Aboriginal communities, and is not aware of any communities that intend to negotiate such agreements. Given the time it took to negotiate the Tiwi Legal Agreement, it is very unlikely that any other communities that wish to negotiate such an agreement would have been able to do so in time to be included in this trial.

The CRCATH expected that the trial be conducted according to the principles outlined in the National Statement on Ethical Conduct in Research Involving Humans 1999, with particular reference paid to the guidelines on research involving collectivities and Aboriginal & Torres Strait Islander peoples. The trial would also need to have complied with the requirements of local ethics committees (including the requirements of Aboriginal Subcommittees of the Central Australian Ethics Committee and the Joint Institutional Ethics Committee).
4.16 Equipment and Supplies

All equipment and supplies required by the trial would be provided from trial funds. Suppliers of office equipment, information services, motor vehicles and medical consumables were identified and preliminary costings performed. In addition to the vaccines and study documentation, the sponsor would also supply equipment for the immunogenicity studies.

4.17 Budget

The following budget estimates were not final at the end of the feasibility study. Options 1 and 2 are included to illustrate why the original proposal was discounted. All estimates included a 10 per cent contingency fee and an annual inflation factor of 3 per cent. There was scope to reduce costs in further negotiations, however probably by not more than 5 per cent.

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<tr>
<th>Entire NT</th>
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<tr>
<td>• 3 year recruitment of newborns</td>
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<td>• Booster dose in final year delivered by study team</td>
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<td>• Includes Otitis Media Studies (12 per cent of total)</td>
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<td>• Transition period costs of 5 per cent</td>
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<table>
<thead>
<tr>
<th>Entire NT</th>
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<tbody>
<tr>
<td>• 2 year recruitment of newborns</td>
<td></td>
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<tr>
<td>• Minimalist approach in Darwin urban area</td>
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<tr>
<td>• Booster doses in year 4 delivered by routine services</td>
<td></td>
</tr>
<tr>
<td>• Includes Otitis Media Studies (6 per cent of total)</td>
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<td>• Transition period costs of 5 per cent</td>
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<th>Central Australia + Tiwi Islands</th>
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<tr>
<td>• 2 year recruitment of newborns</td>
<td></td>
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<tr>
<td>• Booster doses in year 4 given by routine staff</td>
<td></td>
</tr>
<tr>
<td>• Includes Otitis Media Studies (4.5 per cent of total)</td>
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<td>• Transition period costs of 5 per cent</td>
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Reducing the entry-level salaries for staff, and seeking further in-kind support from Core Partners with respect to overheads in trial centres could possibly have made savings. Given the limited research infrastructure in the NT, a reduction in actual staff numbers was not feasible, particularly given the significant workload expected with respect to Adverse Event monitoring and the need for relief staff. Similarly, reducing entry level salaries would have affected the ability to recruit suitably experienced personnel.

Specific details of the budget are not presented as none reflect study status at the time of this report.
4.18 Conclusions and Recommendations

4.18.1 General Assessment

The initial proposal for an NT wide vaccine effectiveness study, with the vaccine delivered by routine service providers, was not feasible given logistical, financial and quality assurance issues. While the introduction of Prevenar™ was a major influence on the decision to limit the proposal’s scope, there were several other issues that would have taken considerable time and resources to address in detail.

Research infrastructure in the NT is limited, particularly outside of the Darwin region and ensuring a rigorous, well-coordinated trial would have been difficult.

A robust trial of an unlicensed conjugate pneumococcal vaccine is feasible in a much smaller region given appropriate staffing and resources, further health professional and community education and adequate time to prepare for implementation.

4.18.2 Major issues

The major factor that influenced the ability to set up this trial was the potential introduction of Prevenar™ and the consequent need to start the trial quickly. Many of the issues raised during the feasibility study could have been resolved if there was more time to do so, and if the prospect of an alternative vaccine was not on the horizon.

Overcoming the reluctance of staff, suspicion of research and minimising the impact on existing services would have taken considerable resources and time. Similarly, the same issues were faced in setting up the appropriate systems to track children, and test and pilot procedures.

4.18.3 Benefits of the trial

4.18.3.1 Impact on disease

The vaccine has the potential to achieve one of the largest health outcomes achieved with a single intervention in the Northern Territory for some time. If the vaccine effect is similar to the Hib experience, there should be large reductions in the incidence of disease, with substantial gains in general child health and considerable savings in health care costs.

4.18.3.2 Development of research infrastructure

The trial has the potential to develop substantial research infrastructure in the areas that are finally included in the study. Currently such infrastructure is limited. During discussions with service providers in the region, this aspect of the trial was regarded almost uniformly as an important outcome.

4.18.3.3 Employment, education and training

The trial will create several employment opportunities. There will be ongoing education and training in research, immunisation and communicable diseases for a diverse range of health professionals and community members. Plans also include recruitment of local community members to act as liaison staff for their communities on a part-time basis. This should facilitate relationships between the researchers and local communities and provide new opportunities for communities to be actively involved in research.

4.18.3.4 Strengthening of immunisation services

A major benefit would be the enhancement of immunisation services in participating communities. With trial staff actively tracking children, there is potential to improve the timeliness and coverage of the routine schedule vaccines.
4.18.4 Risks

4.18.4.1 Staff recruitment and turnover

Optimal staff for this type of trial would be persons who have both clinical research and remote area health experience. Until recruitment begins it would be unclear whether sufficient staff would be recruited, however it is highly unlikely that enough personnel would be available who have both clinical research and remote health skills; hence the need to ensure adequate and comprehensive training systems. The work would be demanding, physically and mentally, particularly for remote staff and it is likely that staff turnover will have some impact on the trial’s timelines.

4.18.4.2 Community priorities

Events within communities and the local clinics would impact on the ability of teams to administer vaccines. Cultural events, funerals, ceremonies and seasonal movement would affect community consultation, utilisation of community facilities and locating children. Communities may have several other programs running concurrently, and some may not have seen this research proposal as a priority. The outcome could be reduced recruitment, delayed vaccination, protocol deviations and a delay in the time period in which the study could be completed and results obtained.

4.18.4.3 Timing

There is a substantial amount of work that would be required between completion of the feasibility study and study start date. More detailed examination of several issues is required, particularly the timeliness of vaccination of children, coordination of teams and tracking of children, and data management. Similarly the recruitment of sufficient qualified staff, training them in clinical research, cross cultural issues and remote areas skills may be problematic, particularly as it would need to occur over the Christmas period.

4.18.4.4 Impact on existing services

Trial staff would perform the majority of work during a trial, regardless of the design. This does not mean however that there would be no impact on existing services. Almost all routine service providers would at some point have to devote time to the trial. This may involve fielding clients’ questions and responding to their concerns, attending meetings and education sessions, providing information to trial staff, reporting of adverse events, confirming details for remote community visits and, in some places, organising space and accommodation. In the latter years of the study it is likely that existing services would need to complete the trial schedule in some children.

For any study option, there would be additional demands placed on non-clinical services such as medical records, radiology, microbiology, pharmacy and human resource departments. Consultation with key stakeholders in these areas indicated the additional load would be manageable, however routine services would always take priority over any research-related tasks.

The negatives should, however, be balanced against the positives. Participating services would be provided with additional full time staff to implement the trial and support their current immunisation activities. Similarly, there would be additional administrative infrastructure provided in most settings, including information systems, clinic equipment and office supplies.

Overall, a substantial investment would have been made in public health and immunisation service delivery, health infrastructure and personnel in NT.

4.18.5 Limitations of the feasibility study

Due to the size and scope of the proposal, and the diversity of immunisation settings in the NT, there was insufficient time to refine, investigate, and discuss in detail, implementation plans with all stakeholders. In particular, there was insufficient time to assess in depth the variability within and between remote communities and the feasibility of conducting the
study in all settings. It is likely therefore that some issues that would impact on the success of a trial had not been identified.

There had also been no piloting of procedures and/or plans and the scientific protocol still had several unresolved issues surrounding the validity and reliability of some of the secondary endpoints. Many assumptions made in the design phase could not be tested until the trial started; estimates of effect therefore may be inaccurate.

4.18.6 Recommendations

- The proposed Pneumococcal Conjugate Vaccine Trial proceeds in a small geographically defined area only where there is a high level of support for the trial.

- The trial should not be conducted entirely by routine providers; specific resources and staff trained in clinical research should be provided to conduct the trial within, but not by, these services.

- At most, it would have been possible to start a trial in one - two communities only by January 2001. These communities should have had some previous experience with research to facilitate early commencement.

- There should be formal piloting of procedures and implementation plans prior to study start to more accurately assess the study's feasibility.
5. The Consultation Program

The original feasibility study proposal written by Dr Christine Connors stated that “the study team would consult all organisations regarded as crucial to the trial implementation, and a representative sample of community organisations and health services.” Consultation on this scale for a proposed health intervention/trial had never before been conducted in the NT.

The consultation program was designed to be a reliable indicator from health services about their willingness to participate in a future trial if it were to go ahead. An indication of organisational support, as opposed to a firm commitment on their willingness to be included in a trial was sought at the preliminary stage of consultation. It was envisaged that a formal position from service providers would be sought nearer the completion of the study when more detailed information was available.

In the infancy of the feasibility study it was also anticipated that we would have a ‘reasonable idea’ about the level of support for a trial by July, and from this point efforts would be concentrated on a preparation phase. This preparation phase would be used to prepare resources needed to implement a trial; resources such as training manuals, protocols and patient information materials.

However the consultation program was limited by changes in the design of the proposed trial during the feasibility study (see Section Three). People being consulted could not provide firm responses as the consultation team did not have final details about the proposed trial. These directional changes impacted significantly on the consultation program objectives and timetable.

5.1 Aims

The primary aim of the consultation program was to determine the level of interest in and support for a NT trial using an unlicensed childhood pneumococcal vaccine.

The secondary aims of the consultation program were to:

- design resources and materials to support the consultation process;
- design appropriate evaluation tools;
- evaluate information sessions and media used; and
- gather information from service providers in order to contribute to the trial’s implementation plans.

5.2 Staffing

The Consultation Team consisted of people with diverse experiences and expertise including people with both health and non-health backgrounds. It comprised an Indigenous staff majority, consistent with the philosophy of the CRCATH.

It was the intention of the feasibility study that a consultation team would be based in Central Australia and the Top End.

There were difficulties in finding both available and appropriate staff to work on the project. As a result the team based at MSHR in Alice Springs did not start until May. The consultation staff were employed over different periods of time on either a full-time or part-time basis.

5.3 Method

A consultation program plan was drafted outlining the objectives of the program and included a proposed timeline for completion. Fundamental to the objectives was to ensure that not only the managers and executives of health services but immunisation providers and parents were given the opportunity to express an opinion regarding a trial.
The consultation team continually reinforced that they were ‘neutral’ in the consultation process and that our aim was to provide information to enable people to have input into the proposal. It was particularly important to repeatedly emphasise and demonstrate this neutrality by acknowledging all points of view. Many people consulted, particularly THS staff, initially believed that the consultation process was simply a ‘softening-up’ exercise for a predetermined decision and were very cynical that their views would actually be considered.

There are currently over 120 centres providing immunisation across the NT. The consultation team aimed to speak to staff who provided immunisation, or who were potentially affected by the proposed trial. This included staff working in:

- CHCs;
- GPs providing childhood immunisation;
- Hospital staff including paediatric and maternity ward nurses, hospital executive, laboratory, radiology and pharmacy staff;
- AMSs;
- Disease Control Centres; and
- Public health staff.

We attempted to identify and contact all of the relevant stakeholders. A database containing this information was created and made accessible to all the team. Initial contact was a letter from the Director of the CRCATH, Professor Tony Barnes. The letter stated the outline of the initial proposal for the trial, mentioned that a consultation process had begun and provided contact details for the feasibility study team. As we became aware of other interested parties who had not been initially identified, further letters were sent out. By the end of March 302 letters had been sent to individuals or organisations across the NT (see Appendix D).

Information and contact details for the feasibility study were also included in the following publications allowing another avenue for comments regarding the proposal:

- THS newsletter;
- MSHR newsletter;
- Research Matters, the CRCATH newsletter;
- The Northern Territory Disease Control Bulletin;
- AMANT News – the AMA newsletter;
- The Echo – Division of GPs newsletter (Top End);
- Spinifex Times – Division of GPs (Central Australia);
- Indigenous Health Matters;
- On Websites at THS, MSHR, CRCATH and one created for the feasibility study (www.pneumo@menzies.edu.au); as well as
- wide distribution of our own newsletter – Pneumo News Edition 1 & 2

Some of the CRCATH Executive and the Principal Investigator, in collaboration with SB, developed a media strategy and released a press statement regarding the feasibility study. The project gained brief coverage on ABC Darwin radio news and in the NT News (25 March, 2000). The only response was a letter to the Editor of the NT News written by an author who objected to immunisation and any proposed vaccine trial in the NT. No further media attention was sought during the initial phase of the feasibility study, nor later in the study because of uncertainty about the design of the proposed trial.
Consultation commenced in Darwin and then continued in the other four health districts (Katherine, Barkly, Alice Springs and East Arnhem Land). After receiving the letter of introduction, management, executives and immunisation/health providers were invited to attend an information session. Every attempt was made to conduct these sessions in a location and at a time, which was deemed by those invited to be the most convenient. This included several sessions that were conducted outside normal business hours. All but one of these sessions were conducted in the attendees’ own environments such as clinics, offices and hospitals. The initial consultation for the urban-based health providers and management, in all the health districts, was conducted by staff based in Darwin.

The consultation sessions provided a lot of information and every attempt was made to make the material understandable. The target audience needed to comprehend the complex issues and technical information, which was necessary to make an informed decision about the trial. As research previously conducted in the NT was quite different to what we were presenting to the service providers, many of the people we spoke to were faced with issues they had little or no background or experience in, such as clinical research requirements and vaccine development.

Each audience received the same content however the style of presentation was adapted to accommodate specific audiences for example parents. The information provided was aimed at answering the following questions:

• What is pneumococcal disease and how big is the problem for NT children?
• What is an unlicensed vaccine and how are vaccines developed?
• What would the impact of a trial be on routine service delivery?
• What are some of the implications of conducting clinical research?
• Who is the CRCATH?

The sessions were designed to allow time for further discussion and questions. The majority of these sessions took a minimum of an hour and several sessions generated discussion for up to 2.5 hours. The style and content of the early sessions were piloted and the information they contained evolved during the consultation program to respond to people’s expressed needs. As an example, very early in consultation it became evident that people needed more information regarding the CRCATH.

Another important consideration in the design of the materials used was the ‘transportability’ of the presentation as it was intended to ‘go bush’. Most of the presentations were done using a series of slide shows and discussion.

As it was important to evaluate the information sessions an evaluation tool was designed to determine whether the information contained was adequate and audience appropriate. It also intended to establish whether at an individual level, there was support for the concept of a trial. The evaluation tool and slide show was never intended to be appropriate for all audiences as they assumed a level of literacy in English. In some instances the consultation team were able to fill in the evaluation forms on behalf of audience members, after sitting and speaking about the proposal and any concerns. At other times the evaluation of the session relied on the impression gained by the presenter.

It became evident there was a need to provide written material to help people better understand and clarify any issues from the sessions. An information package was created that contained information on some of the issues discussed. The package included the following:

• an explanation of clinical research with descriptions of the different phases of therapeutic trials;
• The Declaration of Helsinki and other information related to ethical considerations and guidelines;
• a series of annotated bibliographies on immunisation, pneumococcal disease and simultaneous administration of multiple immunisations; and
• an article on pneumococcal disease in Australia.34
There were seventy packages distributed to health services across the NT. They were also made available to the Board of the CRCATH. These packages were designed for clinical staff, but they were also considered suitable for some non-clinical audiences as they provided explanations in plain English and used diagrammatic representations.

Consultation with health services in remote communities in the Top End was commencing when the decision was made to limit the proposed trial to Central Australia only. Discussions were held with one remote Top End community council and health centre, and with remote area nurses from nine communities in East Arnhem District. A presentation was also made at a meeting of AHWs from across the region. Other than feedback on changes to the proposed trial, no further consultation was conducted with remote communities in the Top End.

The feasibility study was discussed in a number of larger settings including:

- the Top End Division of General Practice Family Support Day;
- the monthly in-service/meeting of the Top End practice nurses;
- an East Arnhem Land in-service day for Aboriginal Health Workers;
- the Epidemiology Interest Group seminar at MSHR; and
- the inaugural CRCATH Learning Conference.

After the decision to restrict the proposed trial to Central Australia only, a follow up letter from the Principal Investigator, John Condon, was sent on July 26 to all contacts made during the consultation process. It informed them of the decision to geographically limit the trial to Central Australia and discussed some of the implications of the impending licensure of the Wyeth-Lederle vaccine (Prevenar™). There was only one formal response. Interestingly it came from an organisation that we had only met with in a preliminary capacity. This remote Top End community was very interested in a trial despite the possible implications of introducing Prevenar™.

On August 11, a meeting on the proposed trial was conducted in Alice Springs. Representatives from THS (Darwin, Alice Springs and Tennant Creek), Central Australian and Anyinginyi Congress, the Centre for Remote Health, Urapuntja health service and SB gathered to discuss the issues associated with the trial. The outcome of this meeting was taken back to the Board of the CRCATH to facilitate a clearer basis for their decision.

5.4 Results and Discussion

Overwhelmingly people realised we were not there to ‘sell’ an idea but that we were genuinely interested in their opinions and that this information would be passed onto the Board of the CRCATH. Many people we spoke with struggled with the concept that we did not have a vested interest in a particular outcome. Research that is not investigator driven was clearly a new approach for many individuals and organisations in the NT.

Attendance at the information sessions was approximately 60 per cent of all invitees. There was greater turnout from service providers than there was from management. It was often difficult to schedule meetings with people, particularly in the remote communities and despite consultation being a priority for the feasibility study it wasn’t necessarily a priority at the practitioner level.

Clinics are regularly asked to interrupt their work and plans for the priorities of people coming into the community. One remote Top End community had had 200 visitors in a three-month period, all with ‘priorities’ for the community to discuss.

There was only one written response to the initial letter from Professor Barnes. This came from an AMS in the Top End. Despite hundreds of contacts made, and sessions conducted, very few individuals or organisations contacted us to discuss the trial further or to organise information/consultation sessions.
The Consultation Team noted there were similar concerns, questions and comments being raised almost uniformly in all information sessions. Individually completed evaluation forms (n = 124) indicated that 55 per cent of respondents had specific concerns or questions regarding the proposal; only 45 people actually recorded their concerns on the evaluation forms (Appendix E). While the meetings often generated lively discussions, many concerns were not documented on the evaluation sheets. Some people indicated they had had their concerns addressed during the session.

The majority of comments related to:

- research and how it is/was conducted;
- how the trial would be implemented;
- issues surrounding the safety and vaccine development;
- general issues surrounding immunisation; and
- historical, environmental and ethical concerns underpinning the consultation process.

People had a high degree of scepticism and cynicism about the feasibility study and its aims. Many people we met with were doubtful that their opinions would be listened to, reported on or counted in the decision to proceed or not with a trial. Some immunisation providers were spoken to on many occasions, and when the consultation team were able to revisit practitioners there was greater understanding and information exchanged regarding the proposal.

The issues that were raised during the process can be broadly addressed under the headings of research, immunisation difficulties, vaccine development, logistical queries and ethical, social and environmental factors. These are discussed in further detail below.

5.4.1 Research

The history of research, conducted on Indigenous populations in the NT and Australia, with little or no regard for health outcomes was consistently raised as an issue of concern. One person described it as “Research/Visitor Fatigue”. Concern was continually expressed regarding clinical research being undertaken in developing countries and on Indigenous populations. People wanted to know exactly where else this (SB) vaccine was being tested. We discussed the process of clinical research, and other populations involved in clinical trials with this vaccine around the world, in an attempt to put the NT trial into perspective. They also wondered if the vaccine could become a licensed product without input from the NT. Many individuals questioned why they were being asked to cooperate with a large pharmaceutical company, what was in it for the company and whether there would be any benefit for communities other than health outcomes.

Naming this project The Feasibility Study for a Northern Territory Pneumococcal Vaccine Trial proved to be a barrier to consultation. As well as being a long and cumbersome title, the word ‘trial’ formed an immediate barrier for some people. Many didn’t want to hear about the proposal if it involved research or trials. Some had specific ideas of what a trial was and were unprepared to acknowledge an effectiveness study as a trial. Hence, they did not want to listen to anything further about the proposal.

Many of the immunisation providers and especially the CHNs were concerned the trial would jeopardise their existing relationship with parents. Immunisation is a small part of an overall well baby check provided by the services. They believed that because they had such a positive relationship with parents that they would be forced into a position to advise parents to take part in the trial or not, and they didn’t want to be in that position.
Box 2. Issues surrounding research.

Why the Northern Territory? – Nurses, Health Workers and management

Too much research has been conducted on Aboriginal people. – All the Indigenous groups consulted

Why isn’t the CRCATH pushing the government to get a licensed vaccine rather than pushing the experiments? – AMS staff

Who will own the information? – Many managers especially within Indigenous organisations

Are the baseline figures right, as to the reasons behind the vaccine? – Board member of a CRCATH core partner.

The Erythromycin trial didn’t work when it was ‘sold’ as the answer; why is this going to work? – Board member of a CRCATH core partner

Can mums and dads be thoroughly informed about the trial? – Uniform concern

Having an immunisation trial undermines the relationship we have with the parents we see. – Some CHNs

5.4.2 Immunisation difficulties

Many service providers were particularly ‘protective’ of their immunisation service and saw it as an integral part of other services they provided. It was often expressed that it was one of the services where practitioners had an opportunity to impact on the health of children, and they didn’t want this threatened by a trial. The Division of General Practice was very supportive of the feasibility study and the concept of an intervention. The Division was, however, concerned that conducting a trial in the Top End would detract from their goal to return immunisation services to GPs. Currently GPs in the Top End provide between 3-5 per cent of childhood immunisation.

Initial consultation with immunisation providers indicated they were concerned about the possibility of the trial interfering with the new NT vaccination schedule implemented in May 2000. Some were concerned that if a trial were to be implemented alongside the new schedule, it would be “destined to fail” or, at least make it very difficult to implement. We spoke with several practitioners who had previously implemented vaccine ‘catch-up’ programs in the NT and gained valuable insight into the difficulties they encountered. One reason for concern was the reported confusion parents had when the Hepatitis B catch-up program was run alongside the Measles catch-up program.35,36

Many providers in the urban areas stated that parents would ‘never’ consent to their children receiving three needles during one visit. In response, a review of the literature examining the research on multiple simultaneous immunisations was conducted.

The majority of these concluded that while parental beliefs are important, the biggest impediment to simultaneous immunisation was the beliefs and attitudes of immunisation providers, both physicians and nurses.17-19,23-25,37-39 This review was included in the information package and distributed to health service providers.
Box 3. Issues raised regarding immunisation

Is it safe to give a child two immunisations in one limb? – CHNs

Parents would be unprepared to consent to three needles in one visit. – CHNs and GP staff

This could deskill our staff if ‘outside’ people (referring here to mobile immunisation teams) are immunising. – Clinical staff at AMS

This sounds like a good idea but I don’t want to give the needles. – Senior AHWs and CHNs.

More needles means more babies crying. – Many Nurses and Board member of an AMS

5.4.3 Vaccine development issues

Vaccine development and clinical research, as with other pharmaceutical products, is routinely divided into four phases. The first three phases must be completed prior to the drug being licensed for commercial use. The first two phases usually involve small numbers of people while the third may include several thousand participants. All trials assess the safety of the product.

Safety of the vaccine was a high priority for all stakeholders consulted (Box 4), and many indicated that without ‘scientific proof’ of the safety they were unprepared to make a decision regarding possible inclusion in a proposed trial. There was universal concern expressed not just about the safety of the vaccine but about how vaccines are developed. A large component of sessions was allocated to discussing the stages of clinical trials and their implications. We produced a simple illustration to assist in explaining the process and where children in the NT may be involved (see Appendix F).

Box 4. Safety concerns

Is this safe? – Everyone

I need more time to think about this and the information. – Senior AHW

A lot more information and education about the vaccine is needed before we can give support. – Aboriginal Community Welfare Worker

What are results of testing to date? – Everyone

More information is needed about the long term risks and benefits. – THS Manager

Are any other strains of Pneumococcus going to develop when we remove the ones that cause disease now? – Many immunisation providers

Would like to obtain copy of earlier trial results. – Program Manager AMS

Need to review research papers. – GP AMS

I want to look at the scientific information. – Medical scientist

I would like more information on safety issues, side effects etc. – General practitioner from a CRCATH core partner

This was a particularly difficult area to address, as early in the process we did not have safety data available for public distribution. Preliminary data were made available to members of the feasibility study in the form of an Investigator’s Brochure. However, this document contained commercially confidential information and could not be made available to people outside the study team.
Given the vaccine's safety was perhaps the most critical issue that the audiences wanted addressed, discussions were held with SB in May regarding the provision and distribution of safety results. Due to commercial sensitivities it was decided the most appropriate course of action was to provide specific organisations with a summary of the safety data. It was anticipated that safety results of more recently completed studies would be available around June 2000. The summary, prepared by SB, was delayed and updated information for selective distribution was finally provided for the feasibility study team on August 11. It was also provided to the CRCATH Board prior to their August 16 meeting.

All parents and organisations involved in a trial, if one were to proceed, would need to have safety information made available to them.

5.4.4 Ethical, social, environmental factors

The consultation process drew attention to a complex range of issues that potentially create impediments to a trial proceeding, and certainly influenced the consultation conducted (Box 4). Underpinning these issues was the history of not only how research has previously been, and in some cases continues to be, conducted but also how decisions are made within and between organisations. Clearly evident during consultation was the issue that many healthcare providers at the grassroots level and management do not see eye-to-eye on many issues or management decisions.

There was a level of suspicion and hostility towards the feasibility process. Many clinicians and middle managers felt that they would in reality have very little influence on the outcome; they would simply be directed by senior management to do as they were told. In particular concerns were expressed by some THS staff that their comments would be stifled, and they would be compelled to “toe the company line” regardless of any potential concerns they had. To address this we approached particular THS management and were given an undertaking that the staff would be able to speak freely, and have their concerns recorded regardless of the ‘official’ THS position. We took this information back to staff and interestingly did not receive any further feedback on their position.

More than one agency we spoke to discussed the potential for the trial to foster a more collaborative approach to service delivery in the NT, particularly in helping to prevent duplication and lack of information and service. Similarly, several people and organisations were both surprised and impressed that they were being consulted at all. The scope, content and quality of the consultation process was received extremely positively, with relationships improving substantially over time as more information was delivered and concerns were actively addressed.

**Box 5. Ethical, social and environmental issues.**

*We will be told to participate regardless of the outcomes from this consultation.* – CCC nurses.

*What story are you going to tell people if not everyone is included – re TIWI Health Board may want it but decision may be to offer it only in the Centre; how are you going to explain this to people eg: some no, some yes?* – Board member of CRCATH core partner organisation.

*Can we accept/rely on the Health Dept for providing this info?* – Aboriginal Medical Services

*Will this end up being up to us to do all the work?* – Many remote area and CCC nurses

*How is the final decision made?* – Almost uniform concern that this is not a community/CRCATH decision.

*What effect does overcrowding, poor hygiene & sanitation and limited health resources have on these illnesses that the vaccine is supposed to fix up?* – Board of CRCATH core partner organisation and Community Care staff.

*What’s in this for the drug company?* – Many managers, nurses, AHWs and Indigenous organisations
Issues such as experimenting on babies and the need for resources to be directed at environmental and social risk factors rather than a single intervention were prominent in early discussions. A few individuals felt that the money directed at this project could have been better spent on environmental or social programs such as housing, education and hygiene. Some of these issues were resolved with further discussion about the role of immunisation in public health, the use of private versus government funding, and size of the health impact this vaccine was expected to have in the NT.

With few exceptions, the seriousness of pneumococcal disease in the Northern Territory was widely agreed upon. Many were surprised at the extreme rates of IPD, particularly in Central Australia, and while they had concerns about a trial many felt that “something should be done to stop our babies getting sick”.

5.4.5 Logistical queries

The lessons learned from discussions with practitioners experienced in mass immunisation campaigns highlighted the need to have practitioners involved in the planning stages for a trial. One of the aims of the consultation process was to gather information on how, with consideration to scientific rigour, service providers considered the trial could be implemented. The objective of this sort of consultative process was to develop a ‘usable’ and sustainable implementation plan for a trial.

As the trial was being designed parallel to the consultation program, we often had limited information to pass on to service providers regarding the details of exactly how the trial would be implemented. This proved problematic as it generated two responses. The first was that service providers felt we were withholding information so when they gave support the “true” details would then be declared. They were suspicious that regardless of the findings from the feasibility study, ultimately all the work of a trial would be done by them (Box 5).

The second was that without the details of implementation, providers were not prepared to give an indication of support or not for the trial. When conducting sessions for clinical staff, it was commonly said there was not enough detail regarding logistics to enable a decision about the proposed trial. We wonder if, initially, a limited consultation should have been conducted in a specific group first, (eg, remote area staff) in order to gain information and develop implementation plans for the wider consultation program? This was a particularly ambitious project that attempted to provide the best outcomes without all the information required at the time of consultation.

**Box 6. Logistical issues**

*Sounds like a good idea but I need more information and I want to know in reality what impact it will have on service delivery.* – THS executive

*I would like to have more information about the “how” issues such as, getting vaccine to such a big area.* – Registered Nurse Tennant Creek

*How will you deal with the issue of migrating children?* – Executive Royal Darwin Hospital

*Will this proposal actually get supported or will the work be done by existing service?* – AHWs and RNs Tennant Creek

*I need more information on how this trial could possibly be carried out.* – CCC nurses (Top End)

*If there are monetary gains from the campaign, can funds be redeployed to boost complementary health services, or will they be absorbed?* – Executive staff, THS.
5.4.6 The View of Parents

It was difficult to gather large groups of parents together to discuss the trial for several reasons, including the changing proposal itself and the decisions about where the trial would be conducted. There was debate about how widely we should be discussing a project, which was continually changing, with the public. It was felt that the mixed messages being received in communities undermined the confidence that people were gaining in the consultation process. We were able to speak with small numbers of parents in individual sessions and, as with service providers, many stated they would need more information before they would participate.

Interestingly one thing we noted was that whenever we spoke to health professionals, they were unable to provide an opinion without suggesting what their view as a parent was. For many their role as a parent was so strong that in some cases we needed to specifically ask them what their position would be as a health professional. On several occasions they indicated that while they thought the trial was a good idea, they would not give an unlicensed vaccine to their child. This is probably in large part related to lack of personal experience with intervention studies in general and vaccine studies in particular.

Individuals within the Feasibility Team often discussed the project with friends and relatives who were parents and, again, opinions varied. Some believed the burden of disease to be great enough that vaccinating their child would be of benefit to the community at large. Others felt the risk of disease in their child was not large enough to outweigh the risks of the vaccine. In some instances, previous experience with disease was a major influence on their support of the trial.

5.5 Central Australian Consultation Program

The Central Australian consultation team commenced work in May, approximately two months after the consultation program coordinator commenced work in the Top End. Some preliminary consultation had already been undertaken in Alice Springs and Darwin.

The consultation team located in Central Australia consists of two members, who are located in Alice Springs at MSHR. Both team members are familiar with Central Australian communities, and have had experience in working in bush communities, either as clinic practitioners or administrators in health services, as well as in other community organisations.

The consultation in Central Australia was not performed as extensively as planned because of the changes in the design of the trial during the feasibility study. These design changes caused uncertainty about the information to discuss with communities, and changes in the priorities and timetable of the consultation program. At several points there was uncertainty as to whether the proposed trial would proceed at all.

5.5.1 Methods

The consultation team consulted with health services in Tennant Creek and Alice Springs and with some bush communities. All travel was done by road, which is more convenient in Central Australia than by air.

A consultation plan for remote communities was developed, and sixteen communities were selected to represent all geographic areas of Central Australia. In mid-May a letter was forwarded to these sixteen communities advising them that consultation had begun and that the team would contact them to request permission to visit their community.

This plan commenced with visits to four communities, but visits were suspended when serious concerns were raised about the potential impact of the introduction of Prevenar™ on the conduct of the proposed trial in Central Australia. (see Section Three). Follow-up visits were planned but were not conducted when it became apparent that the large-scale Central Australian trial was unlikely to proceed. After the initial visits to remote communities only telephone contact was maintained until communities were advised in writing that it had been decided to restrict the proposed trial to three areas, only one of which was in Central Australia.
The locations and sites that were consulted are:

- Tennant Creek and Barkly Health Services;
- Anyinginyi Congress;
- Alice Springs-based health clinics, community health services and THS;
- Central Australian Aboriginal Congress;
- Congress Alukura Women’s Health and Birthing Centre;
- Urupuntja;
- Kintore;
- Mt. Liebig; and
- Ltyentye Apurte (Santa Teresa).

The Central Australian consultation team used information materials developed by the team in the Top End. Consultation sessions used a slide presentation and associated explanation to ensure that everyone who was consulted received the same information.

5.5.2 Results

Only a few written responses were received to the initial letter of introduction about the proposed trial.

5.5.2.1 Major issues

The major issues which arose during consultation in Central Australia were:

- the need for full information on the safety and the effectiveness of the SB vaccine, including the results of all previous (phase one and phase two) clinical trials;
- the seriousness of diseases caused by pneumococcal infections, and high number of children affected, and the need for a vaccine to prevent this;
- what impact the introduction of Prevenar™ would have on the trial;
- concern about giving children an unlicensed vaccine;
- the importance of, and difficulty of, parents being fully informed about the vaccine and the trial before deciding whether their children should be involved; and
- whether so much money should be spent on a trial of one vaccine when there are other important priorities such as housing, education and health services.

The most obvious information that people requested was on the safety testing that has been done on the new vaccine. This was being collected in Phase II trials being conducted elsewhere. As comprehensive information was not able to be shared at the time of initial consultations people and communities did not feel comfortable about making a firm decision about participating in a trial. There may be conflict between the commercial confidentiality required by pharmaceutical companies about the location, timing, strategy and results of testing of new vaccines and other drugs, and the need for access to this information by communities and health services considering being involved in clinical trials such as this. While a summary of safety testing information was eventually provided to the consultation team, it would have been of great assistance if this were available earlier. Whilst the consultation program did not confirm that communities in Central Australia would be involved in the trial, some people indicated an expressed interest.

5.5.2.2 Specific communities

Mt. Liebig

Mt. Liebig is approximately 300 kms from Alice Springs and to travel there is by an unsealed road. It takes four hours to drive there. The population of Mt. Liebig is 200.
At Mt. Liebig we met with clinic staff, some women from the community and the community council office clerk. After our consultation at the clinic we departed from Mt. Liebig at 6pm.

We travelled on to Kintore because there was no adequate accommodation at Mt. Liebig, as there had been disruptions there the day before and property had been damaged.

The community was not in a position to make a decision about participation in the trial at this consultation as they required more time to talk about it amongst themselves and with others in the community. We were not able to speak with any community council members as most were away on other business and the town clerk had advised us that initial talks should happen with the health services people at the community first.

The consultation team was in contact with the clinic people after our visit and they requested that we return to talk further with the community council members. We advised them that we would do this as soon as possible. The only ongoing contact was with the clinic team who were advised that a decision was made that the trial was not going to happen in communities in Central Australia.

Kintore

This community is three hours by car further on from Mt. Liebig. It is not far from the Western Australian border and the Aboriginal people who reside here are from the Pintubi nation. People from this community travel frequently to Mt. Liebig and Papunya.

After arriving at Kintore and being accommodated at the home of the coordinator of the women’s centre, contact was made with the clinic staff and attempts were made to speak with the Kintore Community Council. However, the Council office was closed for two days due to major clean up campaigns. But we did speak informally to the Council Chairperson and other members. The community people were very interested to know what the team had come to talk with them about, and they also enjoyed catching up with one of the members of the consultation team who had previously lived in Kintore as the clinic sister.

The women’s centre invited the consultation team to do a presentation in their common room. We also went with the women’s centre when they did their meals on wheels delivery for the day and we chatted with some of the young mums when we delivered meals for the kids who are on the nutrition program.

The team members walked around and talked to men and women, including many young mothers about our project and we took some ladies and one man out bush in the late afternoon and discussed what we had come to the community to do.

The next day the ATSIC Council member returned to the community from Canberra and we had a lengthy discussion with her about the trial. We also presented an information session at the women’s centre and approximately 20 people attended mainly young mothers, grandmothers and some men came to inquire what the information session was about.

Anyinginyi Congress, Tennant Creek

The Consultation Coordinator, Megan Counahan, had previously conducted an initial consultation visit to Tennant Creek. Megan Counahan and Helen Liddle travelled there for the second round of consultation. After introductions a brief was presented on the earlier consultation between CRCATH and Anyinginyi Congress. The meeting was informed that since our first consultation the Feasibility Study had been more recently focused on concentrating the trial only in Central Australia and the Barkly area. At this time the potential impact of the introduction of Prevenar™ had become apparent, and was discussed with Anyinginyi staff. This included whether people would want to continue the trial of the unlicensed SB vaccine or change to the Prevenar™ vaccine.

Some of the clinical staff from Anyinginyi expressed a need to gain data in advance of Prevenar™ being offered before they could make a formal decision about their involvement in the trial. The response of some of the staff was to get a trial going soon as they were very concerned about children in their district.
Issues which were raised during consultation with Anyinginyi staff included:

- the need for safety information about the SB vaccine before deciding whether to be involved in the trial, and information on what other trials are being done with this vaccine;
- concern by some AHWs about giving an unlicensed vaccine;
- the impact of the trial on their workload and the need for additional resources to conduct the trial;
- the need for close cooperation between the trial and primary health care services;
- the high level of disease caused by pneumococcus and the need for a vaccine to prevent this;
- the importance of completing the trial if it commences;
- publicity about the proposed trial would heighten the awareness of immunisation in a town like Tennant Creek;
- it is not preferable to have a single immunisation day at Congress;
- there was some debate amongst the medical staff as to whether the trial staff should give the scheduled vaccines at the same time as the trial vaccine;
- the possibility of a comparative study of the two vaccines, which was thought to be too complex and staff would only be interested in immunising with one vaccine; and
- the final decision about Anyinginyi being involved in the trial would be made by the Anyinginyi Health Council.

Ltyentye Apurte

Ltyentye Apurte is located 86 kms from the town of Alice Springs. It is located south-easterly direction from Alice Springs. Approximately 76 kms of the journey is a long dirt road. The population of Ltyentye Apurte is approximately 300 people, and the main language spoken is Arrernte.

The clinic has two RNs and ten AHWs (four Trainee Health Workers and six registered Health Workers). We held our consultation session in the staff room at the clinic with one RN and three AHWs. As that was the day for the visiting doctors clinic some staff were preoccupied with that clinic session, so were not able to attend our consultation workshop.

Some of the health workers just listened and did not get into discussion about the information we gave about the trial, but, the registered nurse discussed at length some of the issues around a trial. She also said that as she had not been at the community for long, she was not in a position to offer much information, although she did encourage the consultation team to speak with the Ltyentye Apurte Council president, who was overseas and would be back in approximately one month. The Town Clerk was also away and gave his apologies and suggested we return at a later date for a proper consultation.

The consultation team also discussed the proposed trial at the Kerringke Arts Centre and the Spiritual Centre, and with families with whom the consultation team were related.

5.5.3 Urapuntja Health Service

This health service is an independent health service (a member of AMSANT) located three and a half hours north east of Alice Springs along the Sandover Highway. Urapuntja Health Service services many small out-stations from Aparra, the main hub where the store and council offices are located. The Urapuntja health service is further on from there.
We travelled to Utopia community and arrived there after lunch and we sat and talked about the study with the CEO, Kenny Kunoth, and some clinic workers. We talked at the clinic until about six in the evening and then we were invited to stay for the night at a nurse's residence. She was good company and non-fussed about people coming to stay with her at short notice. We did say to Kenny that we were okay about camping out, but he insisted that we stay with Anne Cooke.

A formal meeting was held with the community health council members for the Tuesday morning, which was well attended by a broad selection of younger and older men and women. Mr Kunoth interpreted where he needed to and explained things as we went along in relation to what people should be understanding about the information. There was considerable discussion during and after the presentation.

The community was not in a position to give a definite response as those that attended the meeting would take the information back to other members in the community.

Central Australian Aboriginal Congress Medical Service (Alice Springs)

After a number of informal discussions with the Medical Director, Dr John Boffa, the consultation team met separately with the doctors and the health workers at their routine weekly meetings. We managed to speak to five doctors and the mainly male health workers - two female health workers came into the information session almost at the end of it.

The health workers understood about the proposed trial and there were requests to be involved if it went ahead. Some suggested it would be very interesting to work on such a project. It was clearly acknowledged that pneumococcal disease was very obvious and a major concern with patients who they have contact with.

The doctors appeared keen to be involved. It appeared that they felt responsible for ensuring that patients got the best care available and if this meant that an immunisation trial for a protective/preventative vaccine was being made available then they would be directed by their organisation.

They did inform the consultation team that the Congress Cabinet, which is their management board, would need to make the final decision about whether the trial would be something that the health service would be involved in.

5.5.4 Discussion - Central Australia

5.5.4.1 The consultation process in Central Australia

Community consultation in this study has been a process of discussion with all relevant health care professionals who would either be involved as vaccine providers or who in someway would assist in the trial, as well as parents, guardians or care providers. Key THS personnel were kept informed about all developments and their input was vital to the final outcome of the feasibility study.

Every attempt was made to identify and contact all the relevant stakeholders in the Central Australian region, and communities were forwarded a letter informing them of the initial proposal of the feasibility study. Similarly, sessions were conducted in suitable locations and at times convenient to the people being consulted. This often meant having sessions in more than one location on a community. People were sometimes spoken to in small groups as well as individually. Much of the consultation was done initially at the community clinic, and contact was made with community people by firstly talking with health workers, health professionals and community health council members.

Because of limitations of time and resources, the consultant team was not able to consult with all communities. An information package and newsletter was forwarded to as many as possible.

Difficulties with the consultation process in Central Australia

The consultations that were carried out were inadequate for the communities to formally respond or make an informed decision as further visits by the consultation team to those same communities needed to occur.
Whilst there had been follow-up phone contacts with the few communities that were consulted, those people have needed a longer time frame and more information to make an informed decision about whether they were prepared to be part of a trial. Some of their requests for information only had limited responses because some information was not readily available.

There was a level of uncertainty that hindered the continuation of the consultation. The Central Australian team believed that if consultation was allowed to happen as originally planned, then maybe some of the issues may have been clearer and provided the evidence that may have been helpful in assisting to make the final decision on the study.

There were several factors that hindered the conduct of the consultation program in Central Australia. The most important of these was the changes that occurred in the design of the trial, which caused uncertainty about what information to give to people, delays in the timetable, and the need to revisit people to tell them about changes.

There were also some internal administrative issues that could have impacted on the consultation if it was happening at full capacity. Inadequate administrative support in Alice Springs was a significant impediment to the consultation program. During most of the program the MSHR office at Alice Springs was not operational and support from Darwin was slow and inadequate. Fortunately, the Central Australian consultation team was a tolerant, patient team and would just improvise if things did not happen as expected.

The Central Australian team believed that if consultation was allowed to happen as planned, then maybe some of the issues may have become clearer and provided the evidence that is required to make the final decision on the study. The consultation team states that consultations carried out were inadequate for the communities to formally respond or make an informed decision as further visits by the consultation team to those same communities needed to occur.

Conclusions - Central Australia

Community consultation, whilst limited, has been a process of discussion with all relevant health care professionals, as well as parents and guardians. Relevant health services personnel were kept informed about any developments during the feasibility study and their input has impacted on the direction of consultation as well as the final outcome of the feasibility study. Throughout consultations the team evaluated each session and followed up any issues or concerns or requests for further information, and provided information to the design and logistics section of the study.

The community consultation and individual informed consent process must ensure that the precise information is given to people and that people clearly understand what they are consenting to. It must be clear that people understand that this is a trial and that the vaccine is an unlicensed vaccine. We need to ensure that this process is done with absolute accuracy. The research project needs to ensure that a broad selection of people have been involved in developing and testing information materials and the community consultation and informed consent process, especially those people who have worked with informed consent before.

Any publicity (media, videos) must deliver the message so that people can relate to the information being presented. Information kits have to be easily understood but have all the complex issues fully explained. The language in the informed consent package must be precise and where possible explained in people’s own language if they choose.

In conclusion the experience in working on this feasibility has been both interesting and challenging, and it felt as though we were, in effect, part of a team working towards the same goals, although we were geographically located in Central Australia. Lessons have been learnt and a wealth of knowledge has been acquired. The only frustrating part of the study was the constant level of uncertainty, but we do acknowledge that this is all part and parcel of a feasibility study. It must also be acknowledged that throughout the study there existed a common respect for the individual’s input and opinions. This was certainly critical in this type of study.
5.6 Conclusion - overall consultation program

Overall there was a wide reaching and general level of interest for a NT wide intervention to prevent disease, conditional on issues such as vaccine safety, logistics and organisational support being resolved. Despite the initial hesitancy and concerns expressed, there was overwhelmingly an identified need to do something to prevent ‘our children from getting so sick and dying’. It is our opinion the support for a trial is based primarily on concern for the health of children, and that it could provide a timely solution to the high morbidity and mortality associated with S. pneumoniae.

The realities of conducting a trial are however different. It would take much more than a general level of interest and support to make it work. There would need to be a high level of dedication to the outcomes of the trial and an understanding of what organisations and individuals need to commit to. For many reasons, this level of commitment was not reached by the end of the feasibility study, the primary reason being insufficient time. For many, creating time for this consultation process was not seen as a priority in their workplace and hence there were several delays in both providing information and eliciting opinions.

It is important to allow time for people to process information, especially when, for many people, we were discussing new concepts and ideas. In order to obtain accurate feedback several visits are needed. When preparing for and conducting a trial there needs to be recognition that service providers, particularly in remote communities, are overwhelmed. As was stated by one health provider who has worked in remote areas of the NT for 30 years “it always takes longer in the NT – that’s the reality.” Similarly, given the NT’s unique healthcare environment, the tyranny of distance cannot be underestimated. On more than one occasion we would travel to places to find that no one was able to meet with us to discuss the trial despite prior arrangements. This needs to be considered when creating a time frame for future consultation.

There have been several positive outcomes, however, other than a determination about a level of support for a trial, including:

- raising the profile of the CRCATH and its philosophies and objectives;
- increasing awareness about pneumococcal disease; and
- providing an avenue for people to raise and discuss concerns about research in general.

Possibly the most significant was that a vast number of individuals and organisations had their say and their concerns addressed; to some extent overcoming the suspicion of research and some of the barriers to inter-agency cooperation.

Before any trial commences further extensive consultation, preferably conducted with staff from the communities involved, would be needed. This information should include a protocol and up to date safety information and reflect exactly what would be expected of communities, clinical staff, parents and children. Similarly, given the sensitivity of the issues, it is important to have a process which is as transparent as possible. In the trial in the Navajo population, the team there actively avoided using the word ‘research’ (except whilst obtaining consent) in an attempt to reduce the negative connotations associated with the process; it was known as the Pneumococcal Project (Scott Katz, US Field Director, personal communication).

The difficulties of recruiting staff for this project did not provide an optimum environment to conduct consultation in the time allocated for the study. Particularly during the first two months, the time available was rapidly passing without the resources to do the work. The feasibility study team would also have liked greater contact with particular people and organisations but we were unable to schedule meetings. People in all areas have increasing demands on their time and, in order to have effective consultation, there is a fundamental need to respect those demands and create a time frame for consultation to reflect this. The time available was insufficient to accomplish this to the degree required by the proposal. Despite the difficulties, the consultation process has been valuable and many lessons have been learned that will contribute to future proposals of this nature. Not the least of which is how to structure and initiate the consultation itself.
Is there support for, and interest in, a vaccine trial in the NT? There is certainly widespread interest and a considerable level of ‘in principle’ support, subject to the final design and implementation plans for the proposed trial. As evidenced by changing opinions over time, the more often organisations and individuals were approached, the more likely it was that many of the barriers identified early could possibly have been overcome. There are however some areas where the level of interest and support is substantial and hence they are ideal candidates for smaller scale studies.
6. Informed Consent

This trial posed several major issues regarding ensuring that parents had been given and understood sufficient information to make a well informed decision about whether their child would participate in the trial.

The nature and severity of pneumococcal disease in the NT, including the differences in risk for Aboriginal and non-Aboriginal children in Central Australia and the Top End, would have to be explained. This, however, would probably not be a major difficulty, particularly for Aboriginal people, as the diseases caused by pneumococcus are so familiar to them. However, several complex issues about the vaccine and the trial would have to be explained, particularly because the SB vaccine is an unlicensed product, specifically:

- what a vaccine is, the preventive rather than curative effect of vaccines, and the expected effects and limitations of the SB pneumococcal vaccine;
- the difference between a licensed and unlicensed product, and considerable detail about the safety testing conducted on the SB vaccine; and
- the Therapeutic Goods Administration (TGA) Clinical Trial Exemption (CTX) approval, which assessed the safety of the vaccine.

In addition, the communication process would be more complex with this trial than with most others because of the diverse nature of the NT population, e.g.:

- communication would have to be with community leaders and parents in multiple Aboriginal language groups;
- communication would also be required in several overseas languages for immigrant parents; and
- many Aboriginal community leaders and parents do not have a high level of literacy, so verbal and visual communication methods would be required in addition to written information, and a method to document consent that would be suitable for non-literate people would be required.

It was apparent that the community information and informed consent process would be considerably more difficult than in other large vaccine trials because of the nature of the NT population. It would also be more difficult than for other research projects conducted in the NT because this project would involve many different Aboriginal groups as well as non-Aboriginal people. The ability to conduct an adequate informed consent process would be as important to the success of the trial as any other aspect of design and implementation, and would be vital to obtaining and maintaining community support.

One of the major tasks set for the feasibility study was therefore the development and testing of an informed consent process that would work for:

- people who speak English as their first language;
- people who are not fluent in English but speak an overseas language;
- Aboriginal people who are not fluent in English; and
- both literate and non-literate people.

6.1 Aims of the informed consent program

The initial aims of the informed consent program were to:

1. undertake a literature review of research on the issue of informed consent in research projects, particularly those involving Indigenous peoples;
2. identify the best available model of an information and consent process, that would be flexible enough to be effective for the diverse groups involved in the proposed trial;
3. develop information materials, a consultation method and consent process specifically for the proposed trial, based on the model identified; and
4. test this informed consent process with Aboriginal and non-Aboriginal people, and modify it if required.

There was only a short time available for the feasibility study, and the start to this part of the project was delayed because suitable personnel could not be found initially for this work. When this part of the project did commence it was restricted by the inability to find an experienced social science researcher, and the changes in design of the proposed trial during the study. As a consequence, the initial aims were modified considerably, and the scope of this part of the feasibility study reduced.

The final aims were therefore to:

1. identify the best available model of an information and consent process, that would be flexible enough to be effective for the diverse groups involved in the proposed trial; and
2. develop information materials about pneumococcal disease and pneumococcal vaccines, but not about details of the trial implementation.

Development of specific information and consent materials and processes for the trial could not be completed during the feasibility study because the design of the trial was not finalised until the last week of the feasibility study. Detailed implementation plans would not be developed until after the completion of the feasibility study. Considerable further work is required to develop, test and refine information and consent materials and processes during the preparation phase of the trial.

6.2 Resources

The informed consent project team comprised:

- Kaye McGuinness (full-time May–August)
- Norma Benger, of the Aboriginal Policy and Health Education Unit at the Menzies School of Health Research (part-time July–August)

A social scientist with experience of research with Aboriginal people could not be found within the time available to this project. The research skills required were in areas of cross-cultural communication and linguistics. Several organisations were identified as possibly having the appropriate expertise. Detailed negotiations were conducted with the Research Branch of the Institute for Aboriginal Development in Alice Springs, and plans made for a collaboration with Debra Maidment, the Director of the Research Branch, and her staff.

However, this collaboration was postponed because of changes in the overall direction of the feasibility study, particularly the decision to reduce the scale of the proposed trial and not have the trial based in Central Australia (with the exception of Nganampa). Other organisations were identified as possibly having the appropriate expertise but were not able to contribute to this project because resources were already fully committed. These organisations included the Centre for Indigenous Natural and Cultural Resource Management at the Northern Territory University, the Aboriginal Resource Development Service, which operates principally in Arnhem Land, and Aboriginal Language Centres.

6.3 Method

The methods adopted by the informed consent team were:

- identification of current and recent research projects being conducted by MSHR and associated institutions;
- identification and evaluation of existing information and consent materials and processes used in these research projects;
- interview of researchers about their experiences of conducting an informed consent process with Aboriginal communities and research participants;
- field observation of the informed consent process;
• interviews with AHWs and Aboriginal Liaison Officers in hospitals and health services about their practices and experiences of informed consent processes for clinical procedures with Aboriginal people; and

• interviews with parents and grandparents of their experiences and opinions on the best informed consent processes for a research project

6.3.1 Literature review

A formal literature review was not undertaken as originally planned. A literature search identified a number of papers reporting on relevant projects investigating the issue of informed consent for research projects. A summary of these papers is included in Appendix G.

6.3.2 Existing information and consent materials and processes

6.3.2.1 Written protocols:

Copies of participant information materials and consent forms were obtained from several current or recent research projects:

• Randomised Controlled Trial of Amoxycillin for Persistent Nasal Discharge in Rural and Remote Aboriginal Children (Bailie, Edmond, Leach - MSHR)

• Kidney Ultrasound Study-Child (MSHR)

• Randomised Controlled Trial of Early Antibiotic Use for Prevention of Chronic Otitis Media (Leach, Morris, Yonovitz, Matthews - MSHR)

• Two vaccine trials sponsored by SB (Hepatitis A and Hib vaccines)

The three sets of materials from MSHR studies shared certain common characteristics that appear to be appropriate for use with Aboriginal people in remote communities:

• patient information/consent sheets were compliant with National Health and Medical Research Council guidelines, the ICH Good Clinical Practice guidelines and the Tiwi Legal Agreement;

• both participant information and informed consent documents were drafted in plain English;

• particularly in respect of MSHR projects, the patient information and consent sheet were confined to one page;

• there was minimal use of technical medical terminology;

• there was limited but very good use of graphical illustrations; and

• the information was broken up into smaller paragraphs for clarity.

The team considered the standard format of SB’s patient information statement, spanning five pages, would not be suitable for the Indigenous participants in the trial. While the information in this statement is essential, the presentation and style of standard formats is not appropriate for this population.

These documents are required in this style and format by pharmaceutical companies and international regulatory bodies. However they are not appropriate to adequately inform people with poor literacy, people who are not confident in English, and people who are not educated about and familiar with western concepts of disease causation, prevention and treatment, and numerical concepts of risk. Additional information materials will be required in a style that is effective in this situation.

6.3.3 Interviews with researchers, health professionals and parents

The informed consent team conducted semi-structured interviews with health researchers and health professionals about their experience and practice in communicating health information to patients and research participants, focusing on information about important decisions and requesting consent for clinical procedures or being involved in research projects. The people interviewed consisted of:
• five Aboriginal Health Workers/Liaison Officers at Royal Darwin Hospital, Katherine Hospital and Danila Dilba Aboriginal Medical Service;
• one RN at Katherine Hospital;
• four Investigators for research projects at the MSHR; and
• one Field Manager of a research project at the MSHR

Several interviews were conducted with parents and grandparents. The team believed that getting some general feedback from the parents was pivotal to the trial, as they were ultimately the people who would be giving the consent for their child/children to participate in the study. These interviewers focused particularly on what previous experience the parents had with giving consent for health research or medical procedures. A similarly structured questionnaire to that used for researcher and health professionals was used with:

• Four Indigenous grandmothers and great-grandmothers; and
• three mothers and two young couples, Indigenous and non-Indigenous

6.3.4 Observation of informed consent process:

Seven informed consent interviews were observed with potential participants in two research projects. It was also planned to observe Aboriginal Liaison Officers and AHWs at Royal Darwin Hospital as they assist with communication between doctors and patients about consenting for clinical decisions. However due to the shortage of AHWs at the hospital during the feasibility study this could not be arranged.

6.3.5 Graphical and audio-visual information materials

Several examples of graphical and audio-visual information materials were collected or examined:

• Angurugu Adult Heart/Lung Study video

This video is a short explanation of a heart and lung disease research project being conducted with the Angurugu community. The video is part of the participant information materials for the project.

• Telling it Right video – NSW Health Department

A video designed to educate Aboriginal communities about immunisation, this is a good example of an effective health information package, but is not directly relevant to informed consent about health research projects.

• Healthy Heart video (National Heart Foundation)
• Rheumatic Heart Disease Education Program video
• No More Humbug video (Katherine Language Centre)
• AIDS Tape (Centre for Disease Control, THS)
• Strong Mothers Healthy Baby flip charts (THS)

An additional resource that was recommended but was not located during the feasibility study was a paper and video produced by a linguist, Dr Michael Cook, to improve understanding of the court process by Aboriginal people charged with criminal offences or otherwise involved in the court system. Although not directly relevant to health research, this material may be a useful example of basic cross-cultural communication of technical and procedural matters to improve the ability of Aboriginal people to make important decisions (such as whether to plead guilty or not guilty to a criminal charge).
6.4 Recommended model

The recommended model is based on the Rheumatic Fever education program, developed by the MSHR and Danila Dilba Aboriginal Medical Service.

Basic information content

The information which needs to be given to all study participants includes information about:

- what *S. pneumoniae* is and the illnesses that it can cause;
- these illnesses (meningitis, pneumonia, otitis media both acute and chronic) and their consequences;
- the greater occurrence of these illnesses in the NT, and the risk to NT children, including different risk in Aboriginal and non-Aboriginal children, and in the Top End and Central Australia;
- vaccines and how they can prevent some infectious diseases;
- the new SB vaccine, including the expected reduction in risk of pneumococcal disease;
- the drug licensing process, and the current status of the SB vaccine;
- safety and efficacy studies already competed on the SB vaccine, and the TGA review of safety data in the CTX process;
- possible reactions to the vaccine;
- the outcome measures in this trial, and what will be asked of the participants re follow-up, testing and data collection; and
- For relevant participants, information about the sub-studies being conducted (immunogenicity, longitudinal ear disease study).

Information materials

Three major communication materials are proposed:

- a booklet in English containing the above material, written in plain English style, with illustrations;
- a flip-chart of illustrations and script for oral presentation of the material contained in the booklet; and
- a video explaining and illustrating the same material as the booklet, with voice-overs in appropriate Aboriginal languages.

The script for oral presentations will have to be professionally translated into appropriate Aboriginal languages.
6.5 Evaluation

The feasibility study has not been able to develop and test specific information materials and the informed consent process as originally planned. It is thus obviously necessary that the information materials and informed consent process are piloted and refined during the preparatory phase of the trial.

It is also important that the approach taken is evaluated as it proceeds, both to improve the process during the trial and to investigate the issue of informed consent in health research with Indigenous people.

This project will be one of the largest and most complex health research projects ever undertaken with Aboriginal people in remote areas. The lessons learnt during this project should assist other research with Indigenous Australians, both in the Northern Territory and elsewhere. The feasibility study has not found any research into effective community consultation and informed consent processes in health research projects with Indigenous Australians.

There is a reasonably well-established view of the most effective process, which has been repeatedly stated by Indigenous Australians. It is likely that this process is the most appropriate general approach to be used, but this has not been thoroughly assessed and refined. It should be.
References


Feasibility Study Proposal
for an open trial of the
SmithKline Beecham Biologicals multivalent
*Streptococcus pneumoniae*
conjugate vaccine in the
Northern Territory of Australia

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November 1999
Background

The Northern Territory (NT) has a small, highly dispersed population, with a large proportion of Aboriginal people. This creates increased difficulties in provision of health services. The poor health status of Aboriginal people has been well documented, with high morbidity and mortality from all diseases. Rates of infectious diseases remain extremely high, associated strongly with poor environmental living conditions and overcrowding. Recently chronic diseases in adults such as diabetes and renal disease, have increased dramatically in epidemic proportions. The access to health services in both rural and remote areas of the NT are limited with lower per capita health spending and reduced access to medical services, compared with Australians in urban areas. The majority of clients of remote health services are Aboriginal people, whose cultural values and language diversity further restrict equitable access to Western medicine health services. Even in urban areas, Aboriginal people find increased difficulty accessing mainstream services. On this background of high health needs, limited health resources and a culturally diverse clientele, who are amongst the most disadvantaged group in Australia, health services throughout the NT attempt to provide appropriate service delivery.

Population

The Northern Territory (NT) of Australia has a population of 181,923 living in an area of 1.35 million square kilometres. The population is distributed between two large and three smaller towns and many small widely scattered communities. Nearly half of the NT population lives in or around the capital Darwin. The second major urban centre is Alice Springs in Central Australia with 13 per cent of the population. The three smaller urban centres (Katherine, Nhulunbuy and Tennant Creek) have populations between three to nine thousand, which is 9 per cent of total population. The remaining 30 per cent of the population live in small Aboriginal communities, mining towns and pastoral properties. The NT has a culturally diverse population with Aboriginal people comprising 27 per cent of the population and people from Non English Speaking Background (NESB) a further 20 per cent. According to 1995 estimates, 82 per cent of the non-Aboriginal population live in urban centres, compared with 26 per cent of the Aboriginal population. The non-Aboriginal population continues to have higher mobility than those in larger Australian states.

Health services

Urban areas

In the five urban centres, primary care services are mainly provided by General Practitioners (GPs). Each centre also has a regional hospital providing both outpatient and inpatient care. Darwin and Alice Springs act as referral hospitals for the smaller towns. There are also Community Controlled Aboriginal health services and Territory Health Services (THS) Community Care Centres (CCC) in each of the five main towns. Aboriginal clients mainly utilise Community Controlled health services, although some will visit private GPs or the CCCs.

Remote areas

In remote areas there are a total of 83 community health centres. The Commonwealth government directly funds 8.5 per cent of these services (community controlled) with THS funding the rest. THS are the service providers in 76 per cent of remote health services. The remote health services are staffed by Aboriginal Health Workers (AHW’s) and nurses. Only 15 of these health centres have resident doctors, with the remainder have visiting doctors. Many of the larger communities have small outstations with populations ranging from 20-100 people. Health staff visit from the nearby larger community, although in the wet season in the Top End, these outstations may be cut off from road travel.
Nurses and AHWs provide the majority of primary care in remote areas, delivering some of the services normally provided by GPs in urban centres. Patients will be referred to resident or visiting doctors for further assessment and management. All health staff use standard treatment protocols developed within the NT. Acute and emergency work still dominates the health centre activity, although health staff also run a number of public health programs such as growth promotion in young children, women’s health, chronic disease programs as well as immunisation programs.

Current immunisation services

Service Providers

The vast majority of immunisation services are provided through community health centres (CHC) which are managed by either Territory Health Services (THS), community controlled health services (also called Aboriginal Medical Services: AMS) or other non-government services. Nurses and Aboriginal Health Workers provide the majority of immunisation services. General Practitioners provide < 2 per cent of immunisation services (personal communication Dr. Fay Johnston, CDC), although there is increasing involvement with the introduction of the Commonwealth GP immunisation incentive funding. Some GP practices in urban centres utilise practice nurses to provide these services.

Immunisation Registers

There are two databases containing NT immunisation data. The NT Childhood Immunisation database (CID) is maintained locally through the regional Centres for Disease Control (CDC) and the national Australian Childhood Immunisation Register (ACIR) contains data on all Australian children, reported either from the State/Territory health department or directly by GP’s. The NT has historically had high immunisation coverage rates.(2) Recent data analysis from the NT Childhood Immunisation database showed that 89.3 per cent of children were fully immunised at 12 months for all their vaccines due by 6 months of age.(Analysis of the same data by 15 months showed that 92 per cent were fully immunised, indicating timeliness is reasonable) This is slightly higher than the national ACIR data due to problems matching Medicare numbers on ACIR. The Darwin urban area with the largest cohort of children had the highest coverage of 96 per cent which is a significant achievement with the largest population.(unpublished data, CDC Darwin September 1999)

CID produces monthly recall lists which prompt health staff which children are due for immunisation. Remote areas have active recall systems, usually personal reminders. Urban areas rely on parent recall using their child’s hand held immunisation record. All services promote opportunistic immunisation. Vaccine dates are recorded by health staff on the recall list and sent to CDC for entry into CID and transmission to ACIR. Some health services have computerised systems that produce local recall lists. Most GP’s send data direct to ACIR, which then transmits data back to CDC.

Cold chain

The NT was the first State/Territory in Australia to develop comprehensive cold chain monitoring. All health centres and most participating GPs have dedicated vaccine fridges with either a minimum/maximum thermometer or electronic monitors.

All vaccines are distributed by regional hospital pharmacies with cold chain monitors attached to individual (or groups) of vaccines. CDC staff audit cold chain monitoring twice yearly. Constant monitoring and training of staff is required to ensure the cold chain is accurately maintained.

Training

A nationally accredited vaccine provider course has been provided by the THS Staff Development Branch in collaboration with CDC since 1997. 850 staff have commenced the course of which 60 per cent have completed the course (personal communication Rosy Warden, Director SDB). The course is available for all government and non-government providers.
Immunisation services for both adults and children is a key priority area for THS and is included in business plans with specific indicators and targets. The GP Accreditation program, which many GP’s are undertaking has a specific focus on immunisation services. All health service providers have identified immunisations as an important focus of their health service delivery.

**Previous NT experience with new vaccinations**

NT immunisation providers have previously shown their willingness and capability to incorporate new vaccinations into the schedule.

1. **Infant hepatitis B**

   Universal neonatal HB vaccine was introduced in the NT in 1990 which required adding a second needle to two of the immunisation encounters. This was accepted and promoted by health staff despite initial concern about simultaneous vaccines. A study in Darwin looking at factors influencing the uptake of the first dose of HB showed that staff knowledge and attitudes as well as work practices such as standing vaccine orders produced a significant difference in vaccine uptake(3). This is consistent with other studies showing that physicians attitudes to simultaneous vaccination and poor knowledge of contraindications is an important factor in “missed opportunities”(4).

2. **School age hepatitis B**

   The school age HB “catch up” was aimed at all children aged 6-16 years and was conducted from April 1998 - April 1999. This was a significant program targeting 24,290 children and was conducted as a school based program. Over 41,000 doses were provided, with a very low wastage rate of 110 vaccines destroyed due to cold chain breaks.(0.26 per cent vaccines)

   Vaccine coverage was 77 per cent for first dose, 70 per cent for second dose and 62 per cent for third dose. Staff employed were two nurses as program coordinators (one based in Darwin and one in Alice Springs) and limited administrative assistance. There was very little support offered to remote communities, with corresponding lower vaccination rates. “Catch-up” programs have a significant impact on health services which is greater than the adding a vaccine to the routine schedule(5). The coordinators recommended dedicated vaccine eskies, appropriate administrative support, development of all consent information in multiple languages, read only database available to all health staff, reasonable travel budgets and flexible funding.

3. **Hib vaccine**

   Hib vaccine was introduced in April 1993 for infants, with a “catch-up” for children to 5 years started in July 1993. This involved three doses for children less than 15 months and a single dose for children 15m – 5 years. By the end of 1996, 75.2 per cent of children were adequately immunised and a further 8.3 per cent partly immunised.(6) Of the birth cohort 1993-1995, 91 per cent received the first dose, 84 per cent received second dose and 65 per cent received the third dose. (note: the coverage for the third dose is thought to be lower than actual rate due to data issues). There was very little support for health staff to complete the “catch up” of older children, with a corresponding strain on health services. Remote area staff were very active in promoting the vaccine with limited support. In the urban areas, an advertising campaign, featuring the “Horrible Hib monster” was important in increasing parental awareness and vaccination coverage.

4. **Adult pneumococcal vaccine**

   Epidemiological data from Central Australia and the Top End have both demonstrated very high rates of invasive pneumococcal disease in both Aboriginal children and adults. In 1995 a comprehensive vaccination program for the 23 valent pneumococcal vaccine was devised which included: training for all health staff including hospital staff, development of a vaccine register, production of wall charts listing indications for the vaccine, promotion of simultaneous vaccination with Fluvax™ and making invasive pneumococcal disease a
notifiable disease with special surveillance maintained by CDC. The program was slow in uptake till funding was obtained to employ two nursing staff who acted as regional coordinators. With the assistance of these staff, which involved visits to remote areas and active immunisation support, the coverage increased dramatically from <5 per cent to >60 per cent in older Aboriginal people. However, when dedicated funding ceased, the uptake returned to low levels.(7)

Proposed conjugate pneumococcal trial

Provide SmithKline Beecham’s 11 valent conjugate pneumococcal vaccine to all consenting infants born in the Northern Territory (Total 3473 NT resident children born 1998, 1230 Aboriginal and 2243 non Aboriginal, unpublished data Epidemiology Branch). This would involve a primary series of three vaccines at 2, 4 and 6 months with possible booster at 18 months.

A proposed “catch up” of children aged 6 months -3 years. This would be approximately 8420 children. The catch up immunisation would involve three doses for infants less than 1 year, two doses of vaccine for children between 1-2 years and a single dose for children aged 2-3 years.

The data to be collected will need to determined, but current discussion has focused on the following possible data sets:

Main study outcomes

The main outcomes which SKB would seek information on include:

1.1 Invasive pneumococcal disease (pneumonia, bacteraemia, meningitis)

This was made a notifiable disease (laboratory notification) in the NT in 1995. Prior to this date, studies in both the Top End and Central Australia have documented the epidemiology of the disease. Special surveillance of this disease has allowed an accurate data set, including serotypes to be maintained.

This data set has regular quality assurance to ensure completeness of data sets. This will provide historical comparison to assess rates of IPD prevaccine and post vaccine. Analysis of rates for vaccine serotypes will also be possible. Comparison of rates amongst vaccinated and unvaccinated children should also be possible.

1.2 All cause pneumonia from hospital data sets.

Hospital admission data should be able to identify changes in rates of pneumonia. However, other factors influencing hospital admission may confound data on pneumonia. For example, within the Darwin Rural District the number of hospital admissions for respiratory infection in children less than five years, increased almost three times between 1993-1998(8). Interpretation of radiologically diagnosed in children can demonstrate interobserver variability, and would probably require an independent radiological review of all CXR on hospitalised children for a period prevaccine and during the study.

1.3 Immunogenicity and reactogenicity

Immunogenicity would be an important aspect to be monitored. Previous studies of vaccinations in Aboriginal children have shown reduced immunogenicity to a number of vaccines. A small randomised controlled trial in Central Australia using the polysaccharide pneumococcal vaccine demonstrated lower antibody response when comparing Aboriginal children to non Aboriginal children from Adelaide(9). A study of antibody response to three doses of Hib vaccine (PRP-OMPC) in Aboriginal and non Aboriginal children showed similar response at 4 months, but significantly lower geometric mean titres (GMT) after the booster dose at 12 months. The authors propose that malnutrition in the Aboriginal children interfered with the immune response(10). Hanna has documented suboptimal responses to both hepatitis B vaccine and OPV in Aboriginal children, although there has been a decline in hepatitis B incidence attributed to the vaccine in Far North Queensland(11).
A recent study of the heptavalent pneumococcal conjugate vaccine showed reduced GMT when the vaccine was administered concurrently with DPTa and HbOC vaccines, however as the levels were all considered within the protective range the authors conclude that the difference is probably not clinically significant. (12) It is not common practice for nurses and AHWs in remote areas to perform blood tests on young children. These studies would need to be performed by research staff in an accessible group, probably within an urban setting, or a few large communities.

All vaccine providers report significant adverse reactions to vaccinations as a notifiable disease. However, active monitoring of reactogenicity would need to occur within a subset, probably the group of whom immunogenicity studies are performed.

**Nested studies**

These studies are of specific interest to researchers and health providers in the NT and SB have indicated these would need to be funded as separate proposals which would be linked to, but not be performed by, the trial study team.

**2.1 Eardrum perforation at 6 and 12 months.**

This information is currently not collected in a systematic manner by health service staff. There is good historical data from ear research conducted by Menzies School of Health Research (MSHR). To ensure reliable data, examinations would need to be performed by dedicated research staff in a subset of children.

**2.2 Nasal carriage.**

There have been a few studies within the NT which could provide a historical comparison, one in an Aboriginal community and one large study in Darwin Child care centres. These type of nested studies would need to be provided by research staff with limited involvement of health services staff. There is potential for reduction in pneumococcal carriage of specific vaccine serotypes, and possibly impact on carriage of nontypable *Haemophilus influenzae* which is the conjugated protein.

**2.3 Hygiene practices.**

Interest has been expressed from some Board members of the Cooperative Research Centre for Aboriginal and Tropical Health (CRCATH) in exploring aspects of improvements in health hardware (housing, access to water) and hygiene practices on the impact of pneumococcal related disease when vaccines are or are not used. This may, in part, be incorporated as a nested study.

**Major issues in participating in vaccine trial**

The two main issues to consider in the feasibility study are:

1. Informed consent
2. Impact on health services
3. Stakeholder and community acceptance

**1. Informed consent**

Broad consultation with key stakeholders to explore issues around informed consent would occur during the feasibility study. Although significant research has occurred in the NT, particularly amongst the Aboriginal population, the proposed trial would involve all health service providers in the informed consent process. Written individual consent would need to be obtained from parents/carers of each child participating. Health service providers will have limited time to ensure appropriate understanding and consent, therefore the research team will need to devise mechanisms to facilitate informed consent.
This may involve community discussions, information sessions with Aboriginal Health Boards and the Aboriginal Medical Services Alliance of the NT (AMSANT), multimedia campaigns, education sessions at antenatal clinics, postnatal wards in hospitals, childcare centres and playgroup associations. Information packages for families to facilitate informed consent would need to be developed by the research team. This may include written information, in multiple languages, as well as videos, possibly dubbed into local Aboriginal languages.

These packages could provide information about pneumococcal diseases and the new conjugate vaccine, and possibly information about the usual vaccination schedule. This could improve the knowledge that families have about immunisations in general as well as specific information about the conjugate pneumococcal vaccine.

Individual service providers would need to ensure that parents have consented to the trial, but without sufficient support from the research team, health staff may be reluctant to undertake the full informed consent process thus reducing the number of potential participants.

There is the potential for the informed consent process to cause confusion amongst parents and possibly compromise participation in the routine schedule. Current vaccine coverage and participation is very high (90 per cent) with both urban and rural areas recording high rates. However attitudes and perceptions of Aboriginal parents is unknown and there have been no formal studies in the NT.

2. Impact on service delivery

a) Disease prevalence

The obvious benefit is the potential reduction in invasive pneumococcal disease (IPD). NT Aboriginal children have the highest documented rates internationally, with the incidence based mainly on hospital admissions. Within the community, the rates are likely to be at least five times greater. The efficacy of the Wyeth 7-valent vaccine against the vaccine serotypes was 97.4 per cent. Based on known serotypes for invasive pneumococcal disease from 1994-1998 for children less than 3 years old (140/155 cases were serotyped), the SB 11-valent vaccine would cover 67 per cent of invasive cases in children less than three years. The proportion is higher in non Aboriginal children (79 per cent) than Aboriginal children (65 per cent), although non Aboriginal children only constitute 17 per cent of invasive cases. Assuming the same high efficacy, this would reduce emergency evacuations and hospital admissions for IPD by up to 67 per cent, and should also have an impact on the numbers of children presenting to community health centres with bacteremic pneumonia. The current protocol for Aboriginal children is to diagnose pneumonia on clinical signs and treat with daily penicillin injections. Many of these children would have undiagnosed bacteremic pneumonia. The impact against nonbacteremic pneumonia is unknown. As the disease presentation would be anticipated to reduce, the associated clinic workload should also reduce.

There is a potential for an impact against otitis media. Current Phase III data from the Wyeth conjugate pneumococcal vaccine showed a 10 per cent reduction in acute otitis media, a 20 per cent reduction is surgical treatment (grommet insertion) and a decrease in the number of visits to the doctor and use of antibiotics.

Aboriginal children have significant problems with chronic suppurative otitis media, which begins from infancy. This impacts on educational opportunities because of fluctuating hearing loss. Current management strategies are not very effective. Any positive impact on reducing ear disease would be of major benefit. Amongst the non Aboriginal children, potential impact on otitis media may be of greater importance to parents as rates of IPD are much lower.
b) Clinic workload

The impact of extra vaccinations for health staff will be minimised if the infant vaccinations, are provided simultaneously with the usual vaccine schedule. There will probably be concern about extra needles (see below), but the reduction in disease prevalence should lead to a decrease in the number of injectable penicillin needles. In the Hib vaccine study (10) 63 per cent of the Aboriginal cohort had a respiratory infection requiring antibiotic treatment by 13 months of age, compared with 12.5 per cent of the non Aboriginal cohort.

The “catchup” vaccinations for older children would have a significant impact on health staff. With previous vaccination campaigns there has been limited support for remote area staff, with consequently lower coverage rates. Health staff may be unwilling to divert their limited resources to participate in a trial despite the potential benefits. Extra staff would need to be provided to enable sufficient coverage, particularly for Aboriginal children.

Despite extra resources, it is inevitable that some resources would be redirected to immunisations, with a consequent reduction in time available for other programs. In the remote areas where staff struggle to provide sufficient services, this impact will need to be minimised.

c) Extra needles

The NT schedule is already crowded with the inclusion of paediatric HB. The current schedule involves the following number of needles by 18 months: 12 for Aboriginal children and 11 for non-Aboriginal children (unless risk factors for TB) which are provided at seven separate immunisation visits (including birth). Two new combined vaccines (either DPT-HB or Hib-HB) will be available from next year. If pneumococcal conjugate vaccine is included this will increase the number of vaccines given by two but reduce the number of immunisation visits by one. The number of needles by 18 months would be 14 for Aboriginal and 13 for non-Aboriginal children.

At least two of these visits would require three simultaneous needles. This will probably be a major concern for health staff. In the USA, failure of physicians to give simultaneous needles is a common cause of “missed opportunities” and delayed vaccinations. However, research on health staff and parental attitudes show that perceptions of staff often don’t match parental perceptions and that parents prefer to have simultaneous needles which reduce extra visits with associated costs either financial or time (4,14). Development of education packages and training sessions for staff will need to specifically address these issues, otherwise the impact on timeliness and coverage of the NT Immunisation schedule could be significant.

d) Impact on immunisation services

Health staff would need training sessions about the new vaccine and its potential benefits. Strategies that promote improved overall immunisation delivery would be of benefit both for the trial and the usual immunisation services. A narrow focus on the 11-valent conjugate vaccine may not encourage staff participation.

The infrastructure for vaccine delivery needs to be fully audited to detect gaps in services. Vaccine ordering, storage, wastage, cold chain maintenance, data collection and recall systems should be assessed. Again, the benefits would be for the whole of immunisation delivery and not just the pneumococcal conjugate vaccine.

e) Adverse events

There is the potential for adverse effects. Obviously the expected rate and severity will depend upon results of Phase II safety trials, but initial data suggests minor side effects are common and the risk of serious adverse effects would be rare. Clarification of the medicolegal responsibility and potential liability in the event of a serious adverse reaction is an important issue for nursing staff in particular, although all health staff, including private practitioners such as GP’s will be interested in this issue. SKB as the “official agent” running the trial would be expected indemnify all health services providers participating in the trial.
3. Stakeholder and community acceptance

The issues here are quite straightforward and involve the identification of the full set of stakeholder groups. These will include NT population sub-groups, NT institutions including both government and non-government, and certain national agencies. The level of acceptance of the proposed study will depend to a very large extent on the degree to which the first two issues are satisfactorily covered.

Stakeholder Groups

Besides NT people and their communities (eg towns and rural and remote communities), represented by their councils, other key stakeholders include:

* Aboriginal Medical Services Alliance of NT (AMSANT);
* Territory Health Services: executive and operational management and service providers;
* Aboriginal Health Boards;
* Consumer health groups (eg: Childbirth Education Association, Nursing Mothers Association);
* Non-government health services;
* Council of Remote Area Nurses (CRANA);
* Aboriginal Health Worker associations;
* Divisions of General Practice;
* Aboriginal community councils; and
* Playgroup Associations

Feasibility Study Proposal

The feasibility study must provide detailed information on which the CRC Board member organisations and SKB will base their decision on whether to proceed with the vaccine trial. The three major issues which will determine that decision are:

* whether an adequate informed consent process can be developed;
* how widespread support is for the trial from community organisations and health services; and
* whether the trial be undertaken without significantly reducing the capacity of health services to provide normal services.

These three issues will be assessed by:

1. Informed consent

A consultancy project will be commissioned early in the feasibility study with a group or consortium with adequate experience in social sciences and communication, particularly experience with Aboriginal people in the NT, to develop and trial an informed consent methodology. An effective, designed, developed and tested informed consent procedure must be available by the time the study design is submitted for Ethics Approval. This will determine the time schedule for the development of the informed consent procedures.
2. Resource assessment

A detailed assessment of the resources required for the implementation of the trial, and the impact on existing resources and service delivery, is vital to the planning and costing of the trial, and for the decision on whether to proceed with the trial. The assessment will commence by developing a detailed model of how the vaccine delivery and data collection will be implemented in each type of health service (urban general practice, urban community health centre, urban Aboriginal Medical Service, remote community health centre/AMS), and the management functions in the health service organisations involved. This assessment will include both physical requirements (vaccine fridges, etc), human resource requirements and costs, and also existing service delivery capacity and the impact of vaccine delivery and data collection on existing services.

This will be undertaken by a one or two people with appropriate experience in practical health service work, planning and cost estimation in human service. It is estimated that this sub-project will take approximately three months to complete.

3. Consultation with community organisations and health services

The consultation process must provide the CRCATH Board and SB with an accurate estimate of the level of support for the trial from community organisations and health services that will be involved in the trial. The feasibility study will consult all organisations regarded as crucial to the trial implementation, and a representative sample of community organisations and health services. Consultation with a sample of organisations will be sufficient for the decision on whether to proceed with the trial. The consultation during the feasibility study will not involve communities giving community consent to the trial – that will be sought if the trial proceeds. However, the consultation will include a full information process (subject to changes in details after a decision to proceed), sufficient for community organisations and health services to make a decision to participate.

The consultation phase will only be a reliable indicator of later participation in the trial if a full information/discussion process is undertaken during the feasibility consultations. Extensive information aids will be designed and developed in conjunction with experts in communication methods with the wide range of community groups and other stakeholders in the NT.

Ethical issues

A short time frame to perform the feasibility study and then commence the trial subject to CRCATH and Ethics approval, may cause potential conflict of interest for the feasibility study team. They need to ensure they remain independent of the outcome of the study, yet there will be time pressure to commence activities such as media campaigns and educational publicity material development on the assumption the trial is proceeding. The study team will need to ensure that appropriate feedback is given to all people involved in consultations as the outcomes of the feasibility study.

Informed Consent

The Northern Territory’s population is extremely diverse, with a wide range of cultural origins both within the Indigenous Australian section of the population and also within the non-Indigenous section of the population. There are many primary languages spoke in the NT (70 per cent of Aboriginal Territorians do not speak English as their primary language, with upwards of 50 different Aboriginal languages being spoken in the Territory). In addition there are many non-English speaking migrant groups in NT.

Literacy skills are also highly variable between population groups. Even more importantly, conceptual understandings can differ markedly between groups, with some groups have little comprehension of western medical concepts; for example, there may be poor understanding of vaccines and they may not be distinguished from other ‘needles’. In addition the notion of a registered or unregistered vaccine will not be easily understood or explained to some groups. Added to this the idea of giving or withholding consent for a health intervention, based on assessing available information in an informed way, may be understood to differing extents among the various population groups.
To the best of our knowledge, seeking and recording truly informed consent from parents in all sections of the Northern Territory’s population has not been previously attempted for any health intervention research study covering a cohort of all Territorians. Developing and testing an appropriate informed consent procedure for this study given this background will be a challenging task. To assist in this task, indeed to undertake the bulk of the development and testing work, it is proposed to engage a local NT based consultant (yet to be decided) with a good track record of effective consultation with the various NT population groups.

**Time Frame**

January 2000: recruitment (staff) develop information for consultations, provisional study protocol, anticipated timeline, plan for ethics committee approval

February: initial presentation to CRCATH Board of project plan and timeline

February-April: consultations, develop study options, start costing health services impact prepare preliminary report for CRCATH Board

March: preliminary assessment of ethics issues and preliminary contact with ethics committees

May: availability of Phase II data for conjugate pneumococcal vaccine. Further action dependent upon satisfactory results.

May: present interim report (or progress report) to CRCATH Board. At this stage the CRCATH and SB should have sufficient information to reject proposal if there are clear insurmountable problems. If rejection is not indicated the feasibility study will progress to completion before a final decision is made on implementation of the trial. submit full application to Ethics committees (Top End and Central Australia)

May-June: continue consultations complete costings for health services

July: finalise report including detailed costings, final study protocol, logistical planning, quality control, assessment of baseline data, preliminary work on educational materials and publicity campaigns.

August (at latest): present report to CRCATH Board for final decision feedback to all stakeholders on outcome of CRCATH decision.
References


Appendix B

Prevenar™ – an alternative conjugate pneumococcal vaccine

Discussion of issues considered during the feasibility study

Prevenar™ vaccine

Wyeth Lederle has produced a seven valent conjugated pneumococcal vaccine, marketed under the name Prevenar™, which was licensed in the United States of America on 17 February 2000. Wyeth submitted their application to the Therapeutic Goods Administration for Australian licensing in January 2000, with approval expected by about February 2001. Wyeth’s Australian marketing manager has stated that Prevenar™ should be on the Australian market about three months after licensing.

However, Prevenar™ is a very expensive product – a full course in the USA costs over $US200 per child. In practical terms, Prevenar™ will only be available to the vast majority of NT children when it is funded for free vaccination by either the NT or Commonwealth government.

Australian introduction of Prevenar™

The Commonwealth and state governments are currently considering policy regarding use of Prevenar™ in Australia. The Australian Technical Advisory Group on Immunisation (ATAGI) and the Communicable Disease Network of Australia and New Zealand (CDNANZ) have formed a joint Pneumococcal Working Party to develop a discussion paper on options to implement a conjugate pneumococcal vaccine for Australian children.

This discussion paper was due to be completed by December 2000. It will then be considered by both ATAGI and the CDNANZ. These two groups share a number of common members – it is likely that their advice will be similar if not identical. ATAGI is a ministerial advisory council, which will provide advice directly to the Minister. CDNANZ reports to the Public Health Partnership Group and then to the Australian Health Ministers Advisory Council (AHMAC). The Minister will receive advice from ATAGI much sooner than from CDNANZ. There is no precedent for a joint working party between these two organisations – the co-chair of the working party, Vicki Krause, expects that CDNANZ will defer to the ATAGI process if their advice is similar.

It is hard to predict when the Minister will receive this advice. It is unlikely, but not unprecedented, that he will make a funding decision before receiving this advice. However, there is reason to believe that the Minister, when he does consider the issue, will decide to fund use of Prevenar™ in Australia, although probably only for high-risk children. Any decision to fund vaccination of high-risk children would include Aboriginal children in Central Australia, who are the highest risk group in the country.

It is thus highly likely that the Minister will announce funding for vaccination of high-risk children in mid to late 2001, because of:

- the urgent need for this vaccine;
- the priority the current Commonwealth government places on direct, short-term measures to improve Aboriginal health; and
- the requirement for a federal election by November 2001.

This announcement may be that funding will commence at a later date, perhaps the start of the next financial year (July 2002). However, advice from officers of the Department of Health and Aged Care indicates that funds already allocated for immunisation programs are not fully committed and a Prevenar™ vaccination program for high-risk infants could commence without requiring new funds.
Implementation could not occur for several months after the funding announcement as state health agencies prepare for implementation (advise health services, modify clinical practice guidelines, train immunisation providers, prepare public education campaigns, etc). It is unlikely that immunisation with Prevenar™ would commence in Central Australia before late 2001, and probably not until early in 2002. However it is highly likely that routine Prevenar™ vaccination will commence in Central Australia before recruitment into the SB vaccine trial is completed.

The SB vaccine trial should not commence without a high probability that it will be successfully completed. This will require that most parents in study areas continue to enrol their children in the trial, even after Prevenar™ becomes available. Once routine vaccination with Prevenar™ commences it will not be possible to restrict access to Prevenar™ for any parents who wish to use it. Such a restriction would be ethically indefensible.

**Circumstances under which the trial could proceed**

Assuming that Prevenar™ became available during the recruitment phase of the trial, there appeared to be only one scenario under which it was warranted to commence the proposed two-year effectiveness trial. If the trial had been under way for at least 15 months before Prevenar™ vaccination commenced there would be sufficient data collected and reported from the first twelve months of the trial to assess the early indications of effectiveness.

It is expected that at the end of the first twelve months a reduction in pneumococcal disease will be apparent, although not yet statistically significant. However, by this time health services and parents would be comfortable with the trial implementation and early results would indicate that the vaccine was reducing pneumococcal disease. This may reassure health services and community organisations that it is reasonable to delay an active Prevenar™ vaccination campaign for six to nine months until the trial was completed.

Parents would have to be informed that Prevenar™ was available, and those who chose not to be enrolled in the trial would have to be able to vaccinate their children with Prevenar™ if they so chose. The proportion of newborn children enrolling in the trial would almost certainly fall after Prevenar™ became available, but possibly not to a major extent if there was general support from health professionals and health services to complete the trial.

**Decision on whether to proceed with the trial**

A decision to commence the trial, based on this scenario, would require:

- a high degree of confidence that Prevenar™ vaccination would not commence in the NT until preliminary outcomes data were available from the trial;
- a high level of support for the trial from Central Australian health services, senior professionals and parents, including THS (including regional, rural services and public health management), AMSANT, CAAC, Nganampa, the Division of General Practice, senior paediatricians, public health professionals, community health nurses and Aboriginal health workers; and
- formal in-principle support from several organisations that if the trial was less then twelve months from completion and a disease reduction was apparent when Prevenar™ became available, active implementation of Prevenar™ vaccination would be delayed. Such organisations would include THS senior management, CAAC and Nganampa Health Council.

**Risk analysis re commencement of Prevenar™ vaccination**

There are two major issues about the Prevenar™ vaccine which must be considered in the decision on whether to proceed with the trial:

- the timing of the commencement of Prevenar™ vaccination in the NT
- the likelihood that introduction of Prevenar™ vaccination in Central Australia could be delayed.
Timing of commencement of Prevenar™ vaccination in the NT

A series of Commonwealth and NT government policy development processes, funding decisions and finally implementation processes are required before Prevenar™ vaccination will commence in the NT. These processes are listed below. Central to this process is the decision on funding by the Commonwealth Minister for Health.

Note that the Minister may circumvent this process by announcing funding early, independent of policy advice, as has occurred for other vaccination issues. The most likely times for such an announcement are shortly after the vaccine is licensed, and shortly before a federal election is called.

The current process is:

2. Discussion paper considered by CDNANZ, advice sent to National Public Health Partnership Group (CDNANZ would probably defer to ATAGI if the two group’s advice is similar).
3. Discussion paper considered by ATAGI, advice prepared to Minister (ATAGI is a Ministerial advisory council, advice will go directly to the Minister not through other DH&AC committees).
4. DH&AC processes ATAGI advice.
5. ATAGI advice considered by Minister, probably including consultation with other Commonwealth departments (eg, Finance, Treasury).
6. Policy and funding decision announced by Minister.
7. Agreement on funding reached with NT Govt.
8. Implementation plan developed and implemented by THS Centre for Disease Control, Aboriginal Medical Services and other vaccine providers.

Estimates of possible vaccination commencement dates range from:
- earliest possible: 9 March 2001
- most likely: 2 February 2002
- latest plausible: 9 September 2002

Service providers support to delay an active Prevenar™ vaccination campaign in study areas.

Service providers will have to give in principle endorsement to delaying an active Prevenar™ vaccination campaign in study areas until the trial is completed before the decision on whether to proceed with the trial is taken. The crucial service providers are CAAC, Nganampa Health Council, AMSANT as a peak body, and THS Executive (based on support from management and senior health professionals in Central Australia).

Service providers would require the following conditions to be met before they could give this in principle endorsement:

1. General high level of support for trial in Central Australia
2. Very high level of support for trial from all other service providers
3. Preliminary outcomes data available before (or shortly after) Prevenar™ vaccination commences in the NT

At the feasibility stage, it was estimated that there was approximately a 20 per cent likelihood that preliminary outcomes data would be available before Prevenar™ vaccination commenced, and that it could be up to 8 months after vaccination commenced before preliminary outcomes data was available.
Timing and probability analysis:

To assess the likelihood of preliminary trial results being available before Prevenar™ is introduced, a numeric probability was estimated for each month from July 2001 for the likelihood of Prevenar™ vaccination commencing during that month and the likelihood of preliminary trial data being available before that month.

Probability estimates of the commencement of Prevenar™ vaccination were based on estimations of the likely duration of the various processes that must occur before vaccination commences – licensing, marketing, Commonwealth policy development and funding decisions, and local preparation for implementation.

Probability estimates of availability of preliminary trial results are based on:

- the likely completion dates of the first round of trial vaccinations;
- an assumption that approximately twelve months follow-up time would be necessary before preliminary data analysis; and
- the likelihood that it would take approximately two months to undertake preliminary data analysis and reporting.

These probabilities are very rough estimates only, but they provide an indication of the situation in which the decision on whether to proceed with the trial needed to be made.

Figure One presents these probabilities in graphical form. Figure Two presents the actual probability estimates, and the combined probability that preliminary results will be available before Prevenar™ vaccination commences (the total of column c).

It is estimated that Prevenar™ vaccination would probably commence in early 2002, but preliminary trial results would not be available until mid to late 2002. There was estimated to be only about a twenty percent chance that preliminary results could be available before Prevenar™ vaccination commenced in the NT, and that there could well be a delay of eight months.

Figure One: Estimated probability of timing of introduction of Prevenar™ and of preliminary trial results being available. Estimated probability of vaccination* and availability of preliminary trial results**, by month

* probability of Prevenar™ introduction commencing during each month
** probability of preliminary results being available before or during each month (ie, cumulative probability)
Figure Two: Estimated probability of commencement of Prevenar™ vaccination and availability of preliminary trial results, by month

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## Appendix C

### Participants in the Design & Logistics Program

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## Appendix D

### Organisations and individuals consulted

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Appendix E

Results from information sessions (n = 124)

There were 124 completed evaluation forms completed from a cross section of people who attended information sessions. (Total number attending sessions approximately 170)

Response to question 2
Do you have enough information to make a decision regarding support or not for the trial?

- 44%
- 28%
- 28%
- 9%
- 7%

Response to question 3
Was the style and pitch of the presentation right for this audience?

- 84%
- 9%
- 7%

Response to question 4
If the proposed trial were to go ahead would you be supportive of the concept?

- 61%
- 36%
- 3%

Response to question 5
Do you have specific concerns or questions?

- 46%
- 39%
- 15%
Appendix F

Diagrammatic representation of the stages of vaccine development used during the consultation program
Appendix G

Summary of selected papers on informed consent in health research


Aimed to determine degree if understanding of surgical risk associated with surgical procedure, it also looked at assessing pre- and postoperative anxiety and depression levels. Randomised groups given routine consent or routine consent plus written info or routine consent plus written and verbal info or routine consent and verbal info. Pts undertook 2 “comprehensive “ questionnaires pre-operatively and 6 wks postoperatively. The results concluded that the extra written and verbal material did not improve understanding or the patient’s perception of their understanding. There was no reduction in anxiety levels with the extra information. It was also concluded that simple information was the best approach - Patients have a basic understanding but the intricate details were difficult to comprehend no matter how it was presented.


Aimed to determine if participants had received adequate information - based on the declaration of Helsinki. The participants were followed up, using a questionnaire, 18 months following the end of the clinical trial. The researchers and the participants were unaware that the study would be subject to a follow up investigation. Authors suggest this created a few ethical problems! Conclusions: all but one participant knew they were taking part in a clinical trial (n = 53 in trial, n = 43 were followed up). The quality of information and understanding and recalled varied. The Helsinki guidelines were not met on several occasions. Combining oral and written material provided a better quality informed consent. There were variations between the centres conducting the trial and it was suggested the informers might have caused the deficiencies in perception.

Worth noting that this trial took place in Sweden where written consent isn’t required but written and verbal information must be provided.


Examined the regulations and guidelines of informed consent for federally funded research involving human subjects. Guidelines last underwent major change in 1981. The Human research Ethics group from the University of Pennsylvania made a series of recommendations about reform in three key areas: protecting subject populations with special needs and vulnerability’s, oversight by institutional review boards and regulatory policy.


The aim was to assess the quality of informed consent again using a questionnaire (n = 230 participants 79 per cent responded to questionnaire.) Part of the questionnaire was multiple choice and part was for the parents to answer in their own words. Results showed 73 per cent were aware of study characteristics. The study suggested that socio-demographic status of the parents did not influence participation. 89 per cent of participants felt positive about consent procedures; 25 per cent felt under obligation to participate
in study. Consent was not obtained during the information session for the parents. The investigator for this trial was on call 24/24 to answer questions and additional written material was provided to the parents. 97 per cent of respondents said verbal information was simple to understand 95 per cent said the same of written information. The authors suggest that parental understanding could have been improved with simpler consent forms, adding that adequate measures should be taken to avoid parents feeling obligated to take part.


Objective of the paper was to review literature on comparisons between different methods of obtaining consent for clinical trials. 812 articles were traced to provide a systematic review. Various studies suggest more information and reflection tends to be associated with lower consent rates. There appears to be an optimal level of information to enhance patient understanding, which may reduce anxiety. It is suggested that the increased information is sometimes associated with increased understanding and sometimes it’s not. The authors suggest that the studies are not altogether conclusive and more work needs to be carried out. Recognised limitations of the consent procedures: constraints of time to provide information, people don’t read consent, often avoid discussions with physicians, patients can’t judge whether they want the information until they have received it. The paper suggests consent can be best obtained if information overload is avoided and forms are kept simple. Edwards et al suggest the effects of different formulations of the same information on patients understanding have not been fully investigated in a comprehensive study. Lastly it suggests don’t rely solely on the informed consent process to educate patients about trials.


Should there be a standard of “informed consent” or should ethics be adapted to the culture? This paper looks at attitudes of Gambian people to consent and evaluates the consent process in HIB vaccine trial. The vaccine trial was explained verbally and in an information sheet using the local language prior to consent. Semi structured interviews were conducted to access understanding.

The number of children consented and enrolled in the study (n = 42 848). The trial was preceded with an extensive media campaign and discussions with local leaders. The trial was explained to all mothers who presented at clinics with their children within the first month of the child’s life. The parents also took bilingual information sheets home. When the mother returned with the child at 8 weeks for DTP the study was explained again and then if the mother gave consent the health worker signed the consent form. There was also provision made to enroll those children who had not presented to the clinic during the first 4/52 of their child’s life.

The study examined the views of three differing groups of people consented for the trial. The structured interviews covered areas around understanding and motivation for inclusion or refusal. The interviews (n = 189) were conducted by local health workers with expertise in sensitive interviewing. The interviews were also taped, responses written were directly onto the questionnaire at the time of interview.

Parents sought information from several sources, these sources differed depending on whether it was a rural or urban family. A parent made all final decisions and religious and traditional leaders were only involved in 1 per cent of cases.

The objective was to design and evaluate a structured and rigorous consent procedure. This study involved 49 schizophrenic patients participating in ongoing clinical research. Paper suggests that historically various methods for assessing understanding have been achieved mainly through yes/no self-reported questionnaires. The researchers designed a questionnaire, which took into consideration various legal aspects for assessing patient's capacity to understand informed consent. If a patient did not respond correctly to an item on the questionnaire then that portion was re-explained until the questionnaire could be answered correctly. The consent form was signed when all the components of the questionnaire were correct. The questionnaire was then readministered 7 days later, any incorrect item was explained again to the patient until they reported that they understood or grasped the concept if they didn’t they were excluded from the trial. Results showed that through the implementation of systematic and thorough informed consent procedures many psychotic patients, but not all are able to comprehend and retain critical components.


This is discussion paper surrounding an essay written by Prof. Zimmer and his experiences of participating in phase 1 of a clinical trial for oncology patients. The article discusses some of the issues regarding research protocols, including consent. The paper discusses protocols of phase 1 trials and briefly examines possible future directions.


During the process of conducting a study of a new pertussis vaccine in Senegal, the authors sought to evaluate the incorporation of clear procedures for obtaining individual informed consent from parents. In this part of Senegal all research involving Human subjects had previously obtained consent from community leaders. (The Helsinki Declaration guidelines allow for community based approach to enrolment.)

Population involved in the study composed almost entirely of peanut and millet farmers. The average per capita annual income $100. Literacy rate 30 per cent for men and 10 per cent for women. Infant mortality rate 80/1000. Prior to the trial beginning the village chiefs were told of the trial and by a field physician. An information campaign was launched and individual consent procedures initiated. Each village had a meeting attended by field staff and physicians to provide information about the trial. Presentations were given bilingually and agricultural analogies were made to explain aspects of the trial. Mothers were further informed by interview conducted by local health workers.

Evaluation of the group sessions and the sessions examining individual oral informed consent was conducted. During the group session summary comments reflected agreement in principle to the vaccination and the trial. Although there was a pilot program to evaluate the individual consent process, the interventions were evaluated 2 years after they commenced.

Results showed that women were confused about being asked for individual consent, as they believed they had already given consent at the village meeting. The majority of the mothers who attended the meetings indicated that they didn’t know the details of the study. It was found however, that widespread illiteracy was not a barrier to comprehension.

This is an editorial discussing whether ethical standards on informed consent are dropped to suit another society. Talks briefly about the guiding principles of ethics and very briefly looks at the argument scientific, outcome v's concern for the individual


The article is critical of the commonly given justifications by researchers for not obtaining consent using the same standards as would be used in “Western” cultures. It is suggested the ethical guidelines written by WHO and CIOMS are “unhelpful and vague”. “It aims to argue the inapplicability of arguments that appeal to cultural relativism on factual grounds, rather than the unjustifiability of such arguments on moral grounds.”

It argues the three main reasons that individual informed consent in developing countries is questioned. These are it is culturally and anthropologically inappropriate, potential subjects have questionable competence to give informed consent or that there are insurmountable communication problems and lastly that the need for immediate research findings make the informed consent requirements unreasonable.


It is suggested that despite the requirements for informed consent during research few empiric trials of the actual decision making process exist. The authors created a consent form for a fictitious medication and used it to empirically evaluate the informed consent process. The hypotheses were that consent rates would be equal when patients didn’t receive quantitative information in the consent form and the consent rates would be different when patients did cite quantitative information as a factor in their decision making process. “Drug A100 may work twice as fast as your current medication”

The results strongly suggested what the consent forms contained and what the patient gained from the consent process affected the decision to participate in the research trial. The study demonstrated a significant effect on consent rates when quantitative information was cited, they also believe a broad gap was observed between disclosure and decision - only 45 per cent of patients cited quantitative information in their decision.


Surgical patients (n = 192) were assessed for their understanding of the consent process. All the patients who were enrolled in the study were given verbal information but only half were given “ operation cards”. Research workers independent of the surgical team conducted psychological and psychometric testing on all patients who were then seen by a resident who explained the procedures and provided an opportunity for the patient to ask questions or clarify points. These interviews were taped. Half the patients were given the “operation card” to read for 30 mins at this point and then the resident returned to answer any questions. Patients recall was assessed by a research assistant within 1/24 of signing the consent, further assessments were done on discharge (median Day 5), after 4-6 weeks at outpatient clinics with the final assessment 6/12 later by postal questionnaire.
For the entire cohort, recall was best directly after signing the consent and gradually deteriorated to become significantly worse at the 6/12 assessment. The only significant difference observed was on the day of discharge and those given the cards scored better. Worth noting is that 21 per cent patients considered that they received the most pre-operative information from sources outside the hospital. The authors concluded that they identified a group of people who receive, process and retain information poorly: elderly, pts with low IQs and impaired cognitive function!!


The objective to assess views of parents of babies who participated in a neonatal trial, about feedback of the results. It concentrates on the feedback of trial results to parents of surviving babies. After conducting interviews with the parents it was concluded that it is difficult to pitch information at a suitable level for everyone. There were mixed emotional responses from all the parents interviewed. Parents of babies treated conventionally found results “sobering” and other parents of babies were overjoyed and proud to have been involved in study,. All parents felt strongly about being informed of the study’s findings and emphasised the need for a careful approach in communicating the information.


Paper discussed the historical perspective of informed consent. Toward the end of the paper there is paragraph dedicated to the cultural influence on informed consent. This paper does not raise any new issues. Reinforces that each individual within a culture does not necessary share the same cultural values. Take home message be sensitive of culturally issues.


This is an editorial discussing the role of culture in informed consent. Individual v’s group consent and the affect this has on the legal requirements of consent.
Appendix H

Semi-structured interview with research/clinical staff

I/We would like to talk to you and ask you some questions about your experience and or active participation with the consent process, as in signing up participants who have agreed to be involved in a trial, or a patient who has needed to consent over a health issue.

What communication method was used to get across the information about the trial/health issue, e.g. pamphlet; video; audiotape; flip chart; booklet; densely written document?

What method/s do you think works best for getting across patient information so they can make an informed decision?

How well does the informed consent process work?

What is/was the consent rate?

Time, how long did the informed consent process take?

Did the participants/patients consent immediately after they read/heard the information?

Was/is the informed consent process done using an interpreter?

How many interviews for the informed consent process cancelled?

How many participants/patients withdrew consent partway through

The trial/health treatment?

Physical location, where did the interview for the informed consent process take place?

Were you comfortable/happy about the informed consent process you were involved with?

Semi-structured interview with Parents/Grandparents

I/We would like to talk to you and ask you some questions about consent and your experience with giving consent for your child/grandchild.

Can you recall an occasion when you gave consent?

What patient information were you given before you were asked to consent, for example; pamphlet, booklet, audiotape, video etc.?

Where did you give your consent, for example; in a hospital, clinic, or home?

Were you asked to give your consent immediately after reading or hearing the information, or were you given time?

Were you happy at the time giving your consent?

If you were given patient information about the Pneumococcal Vaccine what would be your preferred model to communicate this information, for example; booklet, pamphlet, audiotape, video?

Any other comments.