menzies school of health research | HOT NORTH Improving Health Outcomes in the Tropical North

Respiratory Health in the Tropics: current and future research priorities

Chris Blyth on behalf of Anne Chang, Josh Hanson, Pam D'Sylva & Simon Smith

JAMES COOK UNIVERSITY AUSTRALIA
TELETHON KIDS INSTITUTE Discover. Prevent. Cure.
THE UNIVERSITY OF SYDNEY
Doherty Institute
SAHMRI South Australian Health & Medical Research Institute
QIMR Berghofer Medical Research Institute
Burnet Institute Medical Research. Practical Action.

Acknowledgements

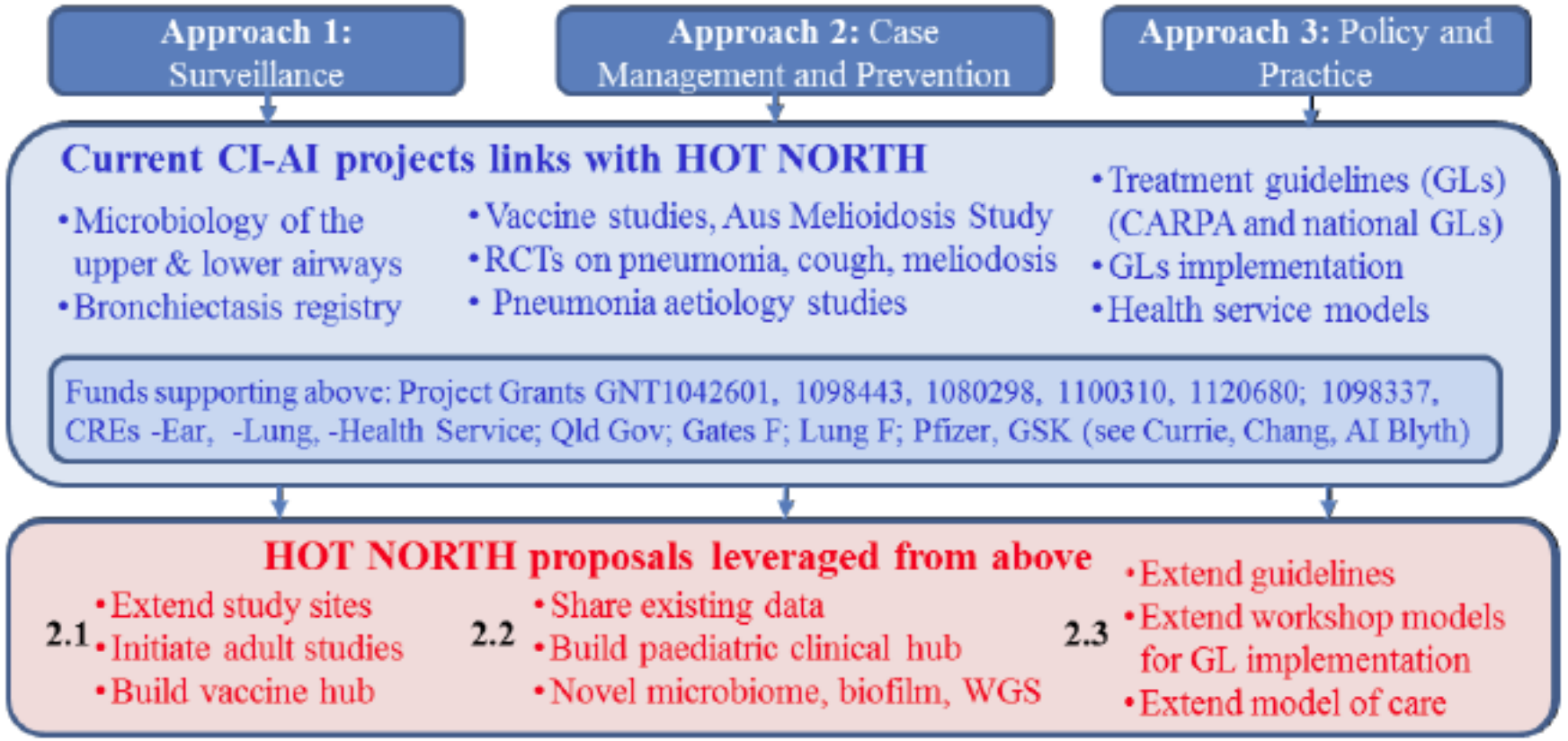
- I acknowledge the Yawuru people, the traditional custodians of the land on which we meet today.
- I would like to pay my respects to Elders past and present.

Background

- Respiratory disorders are:
  - A major cause of global morbidity and mortality
  - The most common non-neonatal cause of under 5y death in our regional neighbours.
  - The most common cause for hospitalisation in Indigenous children and a common cause of hospitalisation in Indigenous adults
  - The most common reasons for GP visits in Indigenous Australians
  - The second most prevalent self-reported chronic condition in Indigenous Australians
- The biggest gap between Indigenous and non-Indigenous Australians is seen in three common conditions
  - Childhood pneumonia
  - Adult pneumonia
  - Bronchiectasis

Respiratory health theme: existing projects

Update on existing projects



Respiratory health theme: existing projects

Update on existing projects

- Hospitalised Pneumonia Extended (HOPE) Study
- PneuCAPTIVE
- Bronchiectasis registry

Hospitalised Pneumonia Extended (HOPE) Study

Primary hypothesis:

A longer duration of antibiotics will deliver better outcomes by:

(i) improving clinical cure rates

(ii) reducing risk of chronic respiratory symptoms / signs or BE

(iii) increasing time to the next respiratory hospitalisation

Primary aim:

To assess whether a longer course of antibiotics, compared to a shorter one, improve clinical outcomes of children hospitalised with severe community-acquired CXR confirmed pneumonia?

Hospitalised Pneumonia Extended (HOPE) Study

Secondary aims:

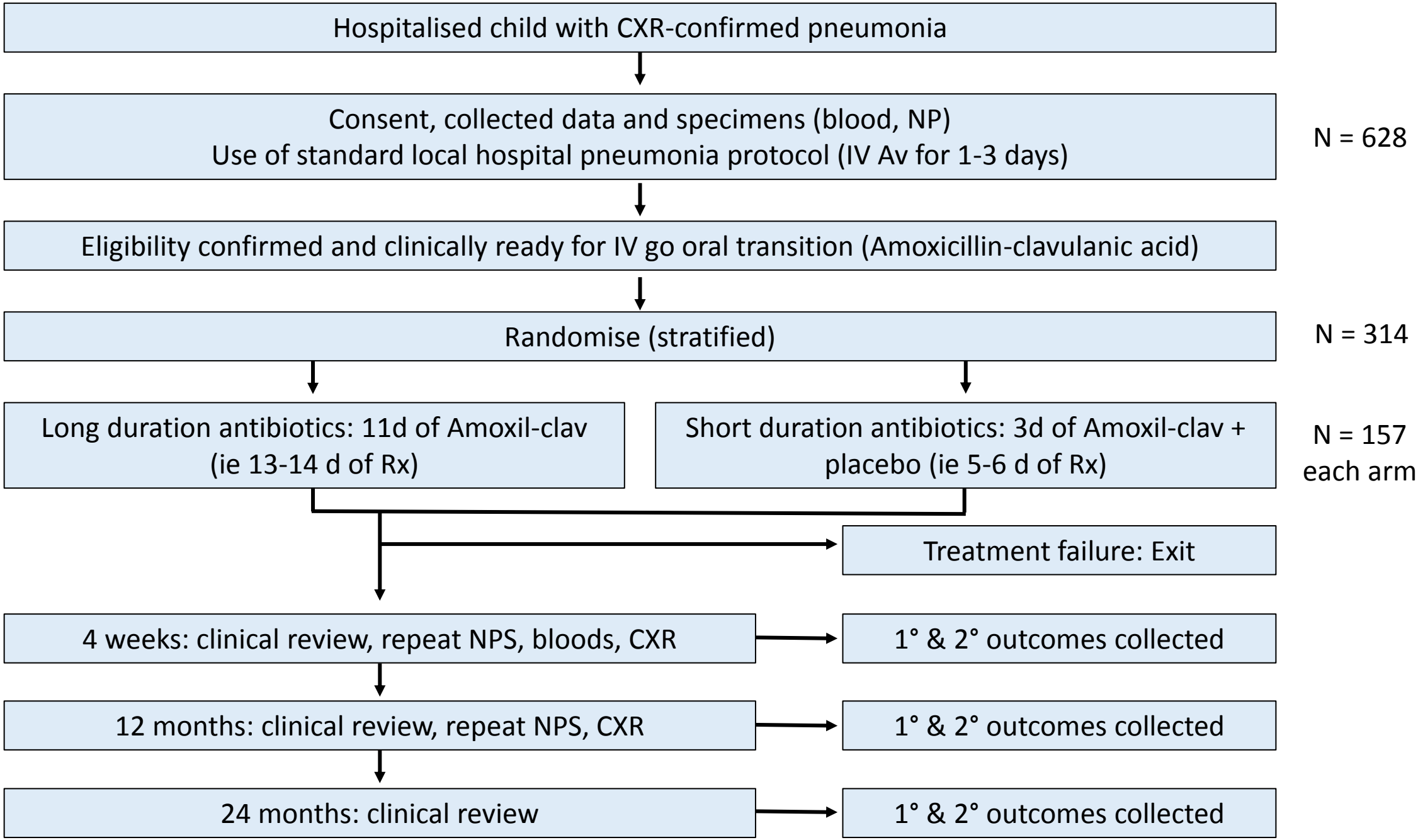
(i) To monitor the effects of the duration of treatment on antibiotic resistance in respiratory pathogens isolated from the nasopharynx (NP).

(ii) To determine the predictors of chronic respiratory symptoms or BE, specifically the contributions of:

a) Host gene expression signatures associated with lower airway bacterial infection

b) Persistent CXR abnormalities following treatment for pneumonia.

- Sites: Darwin, Kuala Lumpur, Kuching, Kota Kinabalu
- Study in progress


Hospitalised child with CXR-confirmed pneumonia
Consent, collected data and specimens (blood, NP)
Use of standard local hospital pneumonia protocol (IV Av for 1-3 days)
N = 628
Eligibility confirmed and clinically ready for IV go oral transition (Amoxicillin-clavulanic acid)
Randomise (stratified)
N = 314
Long duration antibiotics: 11d of Amoxil-clav (ie 13-14 d of Rx)
Short duration antibiotics: 3d of Amoxil-clav + placebo (ie 5-6 d of Rx)
N = 157 each arm
Treatment failure: Exit
4 weeks: clinical review, repeat NPS, bloods, CXR
1° & 2° outcomes collected
12 months: clinical review, repeat NPS, CXR
1° & 2° outcomes collected
24 months: clinical review
1° & 2° outcomes collected

PneuCAPTIVE:

Hypothesis:

Nasopharyngeal pneumococcal colonisation is a useful tool to evaluate the effectiveness of pneumococcal conjugate vaccination (PCV) in resource poor settings

Despite suboptimal uptake, infant PCV vaccination will be beneficial through both direct and indirect effects

Primary Aims:

To determine the PCV13 coverage required to generate a sustained decline in the carriage of PCV13 serotypes in vaccinated and unvaccinated children aged 0-59 months hospitalised with moderate pneumonia.

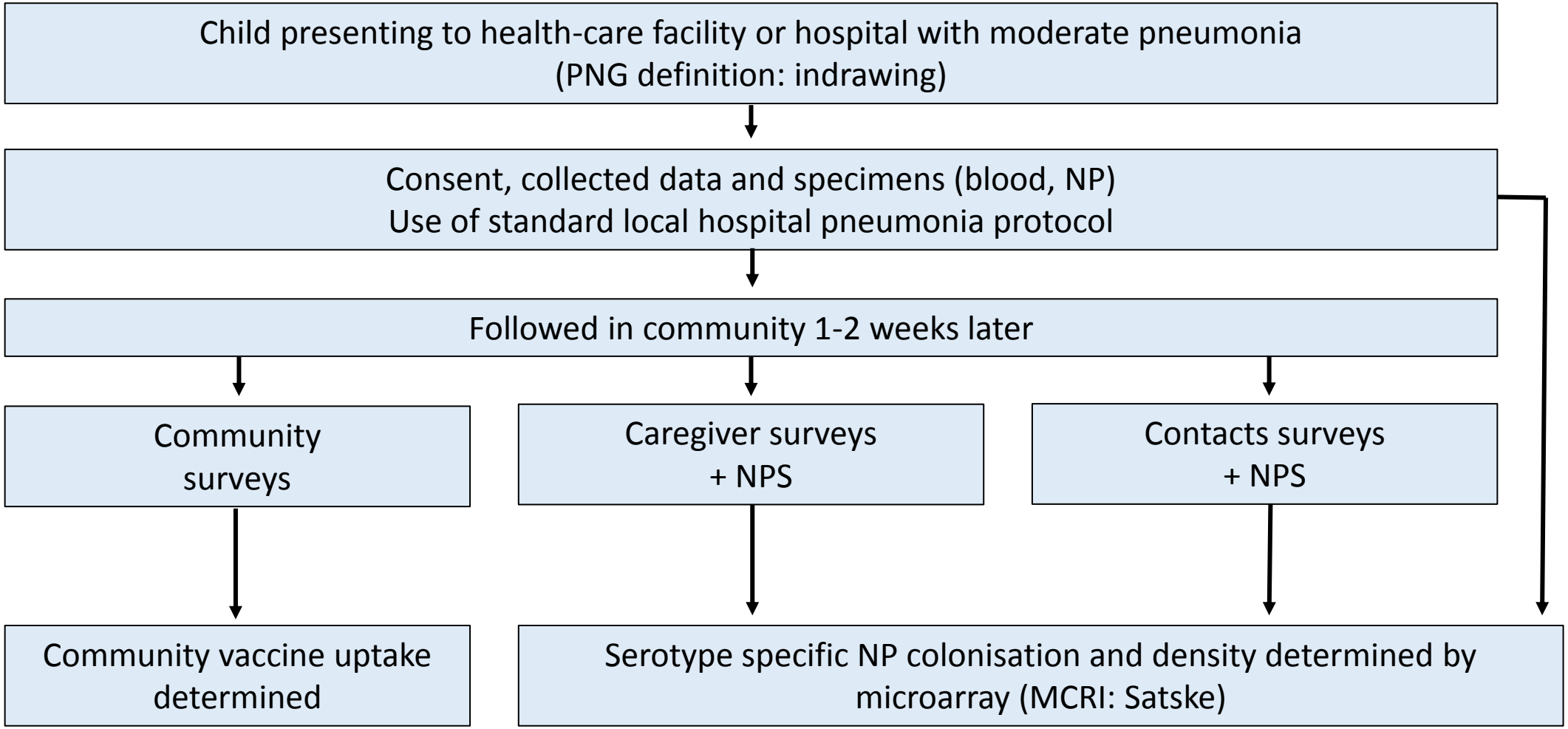
PneuCAPTIVE:

Secondary Aims:

(i) In children aged <5 years hospitalised with moderate pneumonia, their contacts and caregivers:
   a) To determine the proportion with PCV13 and non-PCV13 serotype-specific NP carriage;
   b) To describe serotype-specific pneumococcal carriage density immediately before and following PCV13 introduction
   c) determine the risk factors for pneumococcal carriage

(ii) To compare the median months taken to reach a sustained decline in PCV13 carriage between hospitalised cases and healthy children in the community.

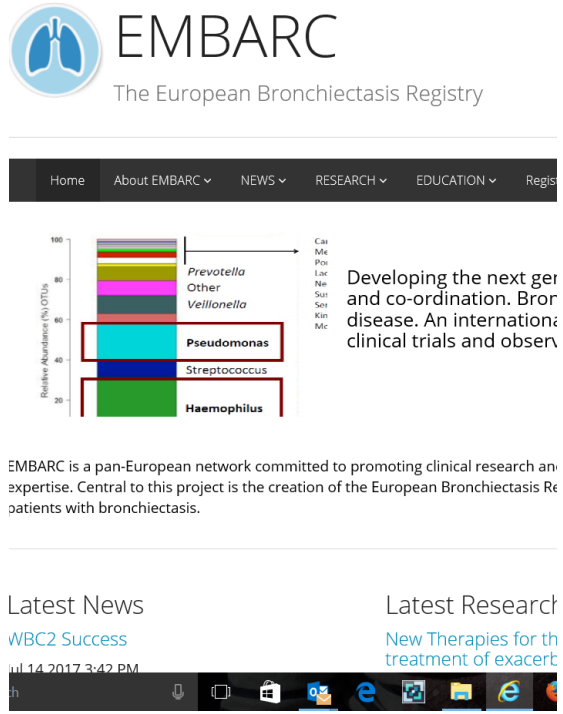
(iii) To continue surveillance of invasive bacterial and viral pathogens in cases of ALRI and meningitis.



- Nested within existing case-control studies (PNG, Laos, Mongolia)
- Current vaccine coverage:

BE Registry

- Managed by Aus Lung Foundation with limited funding
- Terms of Reference established
- Linked to European database (EMBRAC)
- Adults and children
- Current sites (but not all enrolled people as yet)
  - Royal Darwin Hospital
  - Alice
  - Perth
  - Brisbane



Respiratory health theme: new projects

- *What causes pneumonia in children and adults living in tropical Australia*
  Simon Smith, JCU
- *How common is prolonged cough in Aboriginal children living in the Kimberley?*
  Andre Schultz & Pam D'Sylva, Telethon Kids Institute

A prospective study of community-acquired pneumonia in children and adults in tropical Australia
What causes pneumonia in children and adults living in tropical Australia

Simon Smith

Hot North Co-investigators: Josh Hanson, Anne Chang, Chris Blyth

Tropical pneumonia: background

Children

- Admission rates for lower respiratory tract infections higher for Indigenous children
- Indigenous infants are commonly hospitalised before their first birthday
  - Causative organisms not completely characterised
- No reliable tools to predict clinical outcome

Janu EK *et al*. MJA 2014 200:591-4
O'Grady KA *et al*. MJA 2010 192:586-90

Tropical pneumonia: background

Adults

- Aetiology and clinical outcomes across tropical Australia has been incompletely defined:
  - Atypical intracellular organisms are thought to be uncommon
  - Nursing home residents comprise a significant number of admissions

Siemieniuk RA *et al.* Ann Intern Med. 2015 167:519-28
Postma DF *et al*. NEJM. 2015 372:1312-23

Tropical pneumonia: aims & hypothesis

Hypotheses:

1. *S. pneumoniae* and respiratory viruses are common in all populations
2. Atypical bacterial infections are rare
3. *Acinetobacter* baumannii pneumonia is unusual in FNQ and WA
4. The aetiology varies seasonally across tropical Australia
5. Respiratory virus and bacterial co-infection is common
6. Blood cultures are only useful in the most unwell people
7. There are regional variation of high-level penicillin resistance in *SP*
8. It is possible to develop prediction scores in children and nursing home residents

Tropical pneumonia: aims & hypothesis

Primary aims:

1. Identify causative organisms and guide empirical antibiotic choices in tropical Australia
2. Determine clinical associations and outcomes
3. Develop severity prediction scores for:
   i. children
   ii. nursing home residents
4. Produce pilot data to inform future randomised trials

Siemieniuk RA *et al.* Ann Intern Med. 2015 167:519-28
Postma DF *et al*. NEJM. 2015 372:1312-23

Tropical pneumonia: aims & hypothesis

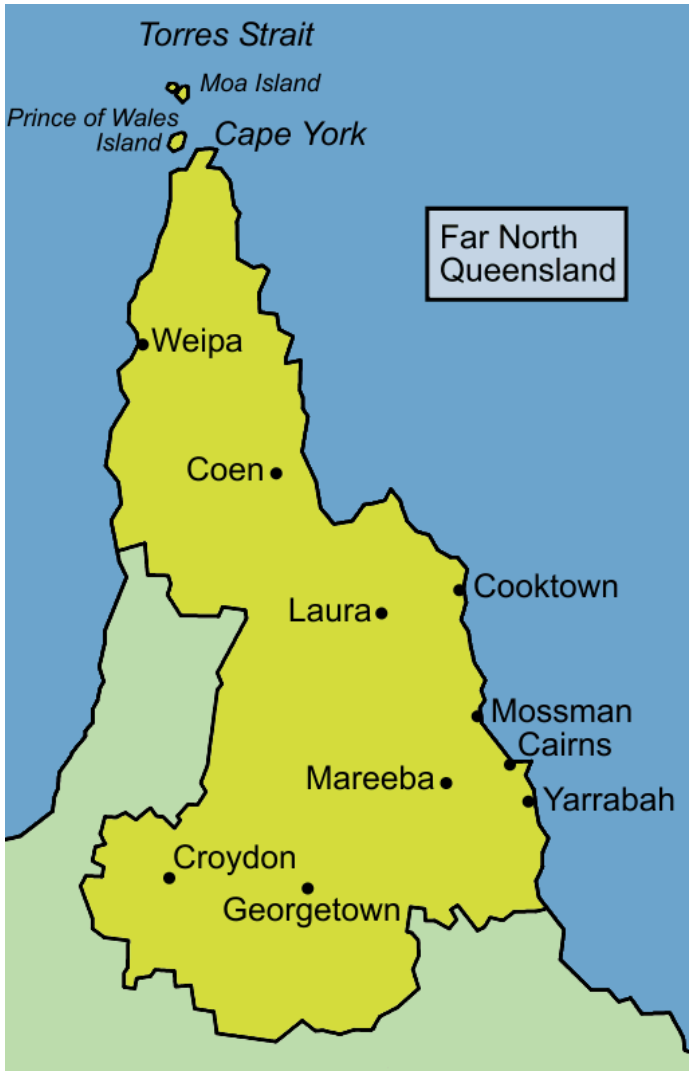
Secondary aims:

1. Identify regional differences across tropical Australia
2. Establish the clinical utility of urinary antigen testing, blood and sputum cultures
3. Determine rates of high-level penicillin resistance in *S. pneumoniae*
4. Identify the causative organisms in people with immunosuppression and chronic lung disease

Tropical pneumonia: methods

Prospective, multi-centre case-control study of children and adults

- Initial sites: Cairns, Thursday Island, Weipa and Cooktown hospital
- Future sites: Darwin, (Broome)



Tropical pneumonia: methods

Inclusion criteria:

Children ≥ 1 months with clinical evidence of pneumonia

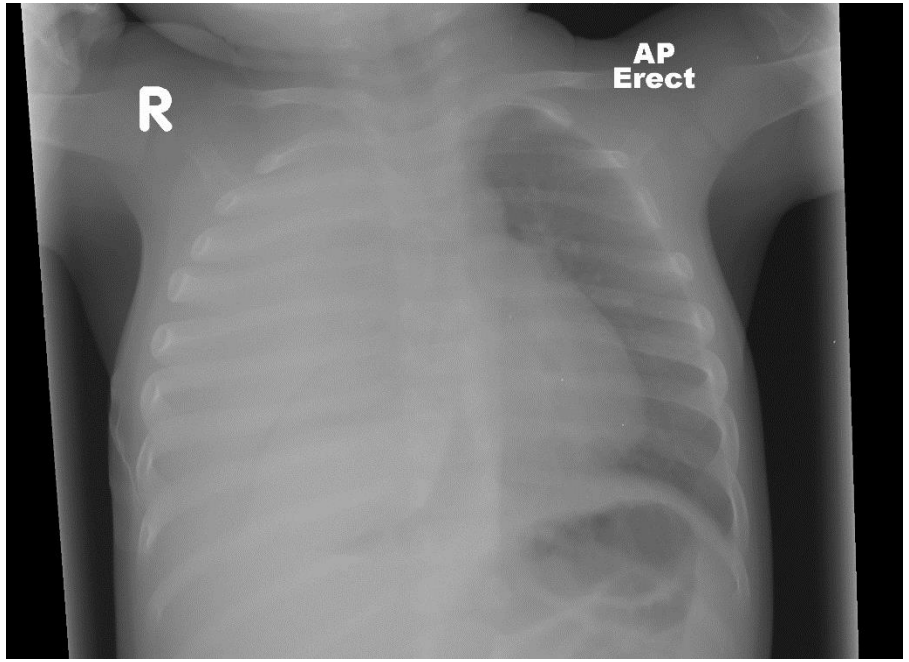
- Fever
- tachypnoea, chest retraction, or abnormal auscultatory findings

Adults with at least two of

- Fever or hypothermia, rigors, sweats
- New cough (+/- sputum production)
- Change in colour of respiratory secretions (chronic cough)
- Chest discomfort or dyspnoea

Xray confirmation within 24h of admission

Recruitment and sampling within 48h of admission



Tropical pneumonia: methods

Data collected:

- Demographics
- Past medical history/comorbidities
- Vaccination history
- Gestation and birth weight
- SMART-COP and CORB scores
- Antibiotic therapy
- Oxygen therapy, intensive care, mortality
- Follow up at 30 days

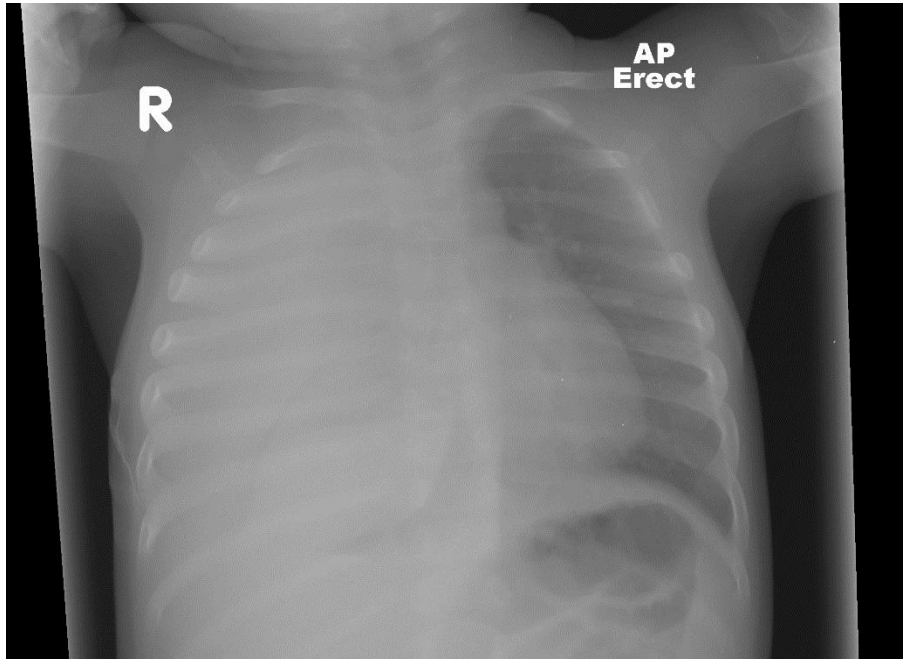
Tropical pneumonia: methods

Microbiological sampling:

- Blood culture
- Acute + Convalescent serology (adults only)
- Sputum Culture (where possible)
- Tracheal aspirate or bronchoalveolar lavage (intubated patients)
- Urine Pneumococcal and *Legionella* antigens
- NP flocked swab and throat swab for PCR

  RSV, adenovirus, parainfluenza (1-3), influenza A/B, rhinovirus, coronaviruses, human metapneumovirus

  M. pneumoniae and *B. pertussis*
- PaxGene tubes



Tropical pneumonia: methods

Control recruitment

- Healthy controls recruited from outpatient clinics and from non-respiratory inpatient wards
- Age and season matched
- NP sampling performed
- NP flocked swab and throat swab for PCR

  RSV, adenovirus, parainfluenza (1-3), influenza A/B, rhinovirus, coronaviruses, human metapneumovirus, *M. pneumoniae* and *B. pertussis*

Tropical pneumonia: methods

Analysis (aetiology):

- Compare distribution of each pathogen in cases and controls
- Univariate Odds ratio (OR) for each pathogen and logistic regression adjusting for demographic factors and the presence of all pathogen
- Population attributable factor for each pathogen

Analysis (predictors of severity)

- Predictors of severity identified using logistic regression

Tropical pneumonia: expected outcomes

To commence November 2017

- Inclusive study
- Assess the validity existing therapeutic guidelines
  - Rationalisation of empirical antibiotic regimens
- Develop predictive scoring systems in children and nursing home residents
- Testing of stored samples may allow identification of novel pathogens

Healthy Lungs for Aboriginal Children in Western Australia

Pam D'Sylva, Andre Schultz

Hot North Co-investigators: Anne Chang

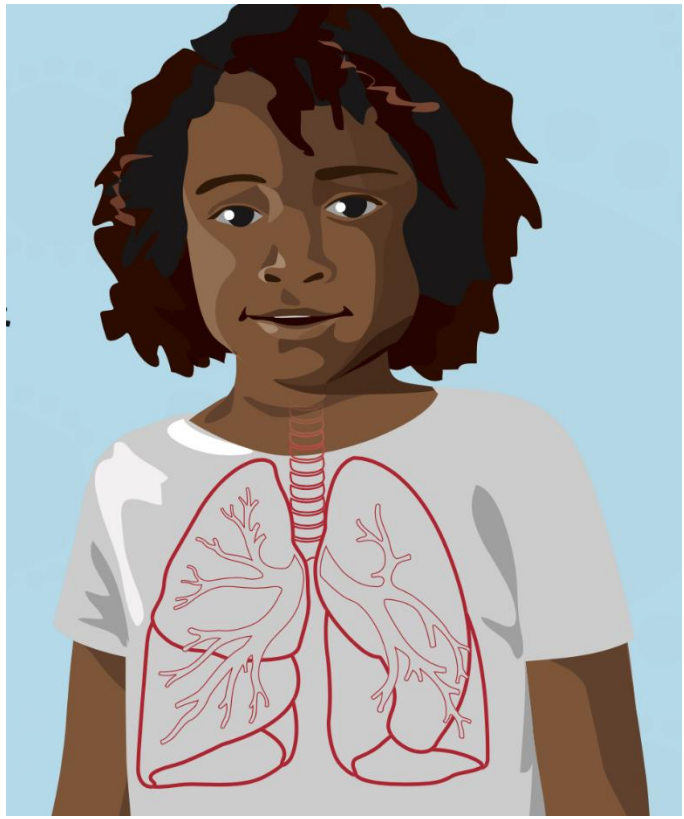


Image courtesy of Menzies School of Health Research

Tackling cough and lung sickness in children

- Part one: “Prevalence of chronic moist cough in Aboriginal children in the Kimberley”

- Part two: “Improving recognition and management of chronic moist cough in young Aboriginal children by carers and health practitioners in Western Australia”

Background

- Respiratory illness is the most common cause of Aboriginal hospitalizations in children.
- The burden of chronic lung disease in Aboriginal adults can be substantially reduced if early lung disease is managed effectively in children
- Chronic suppurative lung disease (CSLD) is highly prevalent in Australian Indigenous populations
  - Estimated prevalence of bronchiectasis in Central Australian Aboriginal children is 1.5%

Chang AB *et al*. Ped Pulm. 2003

CSLD goes under the radar until it’s too late!

- CSLD is a progressive infectious condition that ranges from persistent bacterial bronchitis to end-stage irreversible bronchiectasis
- Earliest sign is usually a chronic moist cough (>4/52)
- Ongoing moist cough indicates lung inflammation and infection
- Normalisation of cough by carers and health practitioners prevents timely assessment and treatment that prevents long-term structural damage

Image courtesy of Menzies school of health research

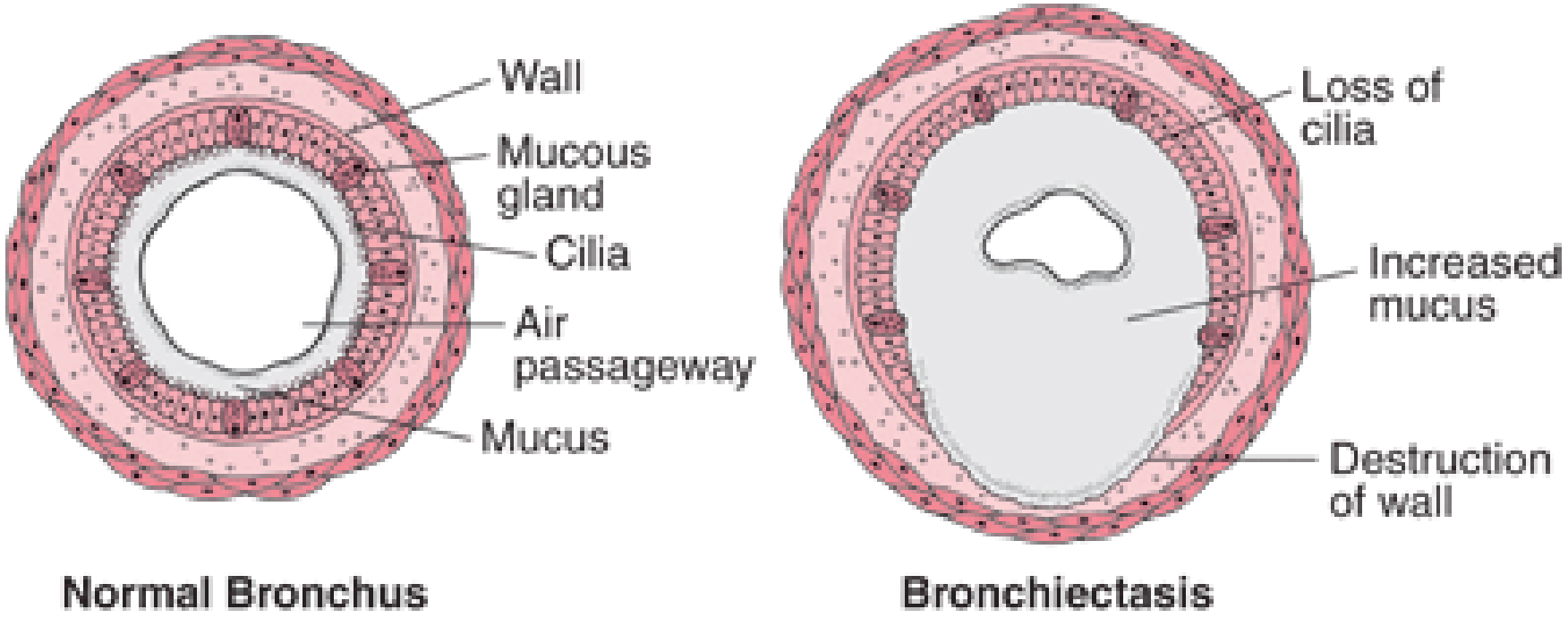
Moist cough often normalised in Aboriginal children

"I would not have thought to mention that she has a cough as she has had a cough since she was 11 months old. In the morning she sounds like a smoker. But she has always had that"

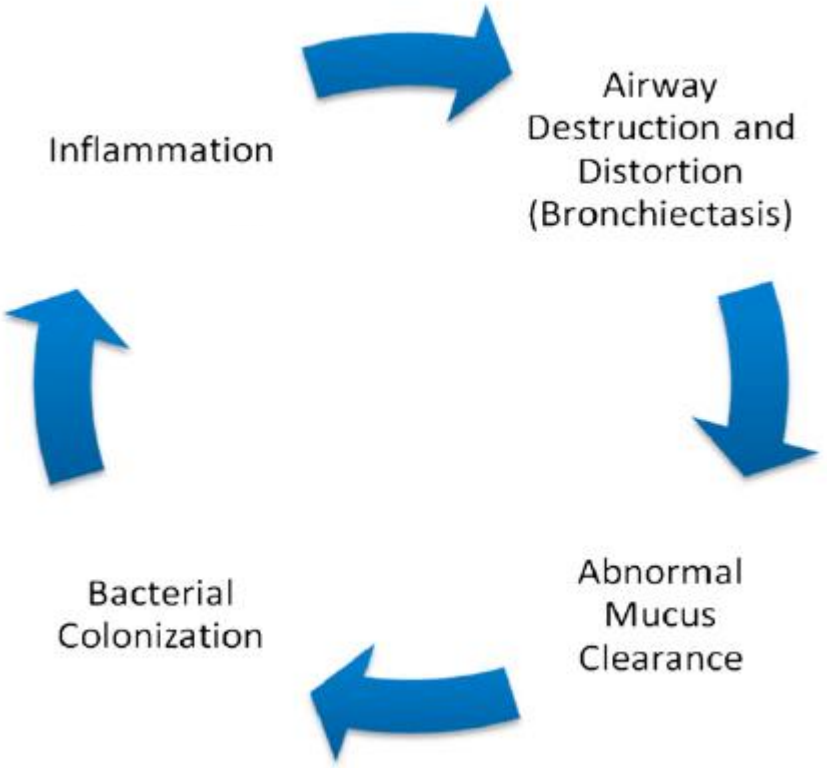
Carer of a child with bronchiectasis

Image courtesy of Menzies School of Health Research

Pathology


Wall
Mucous gland
Cilia
Air passageway
Mucus
Loss of cilia
Increased mucus
Destruction of wall
Normal Bronchus
Bronchiectasis

Vicious cycle leading to CSLD and bronchiectasis



Cole PJ. Eur J Resp Dis Suppl. 1986

Progression

Protracted bacterial bronchitis

Chronic Suppurative Lung Disease

Bronchiectasis

Overall objective

To develop culturally sensitive and sustainable solutions for early detection, accurate diagnosis and timely treatment of protracted bacterial bronchitis (PBB) and chronic suppurative lung disease (CSLD).

AIMS-specific

1.Establish the prevalence of chronic moist cough in the Kimberley.

2.To identify enablers and barriers for Aboriginal carers to seek timely healthcare for chronic moist cough.

3.To improve timely healthcare seeking by carers of Aboriginal children through an intervention informed by knowledge from aim 2.

4. Identify and understand the enablers and barriers for primary health practitioners to provide optimal healthcare to Aboriginal children with chronic moist cough.

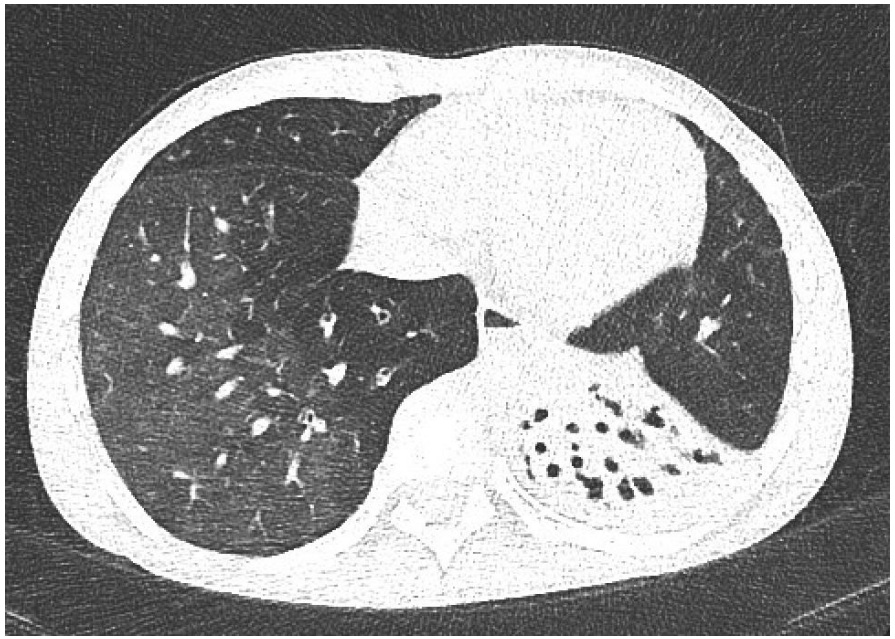
5.To improve healthcare of Aboriginal children with chronic moist cough by improving the uptake of evidence-based guidelines on chronic cough &CSLD by primary health practitioners.

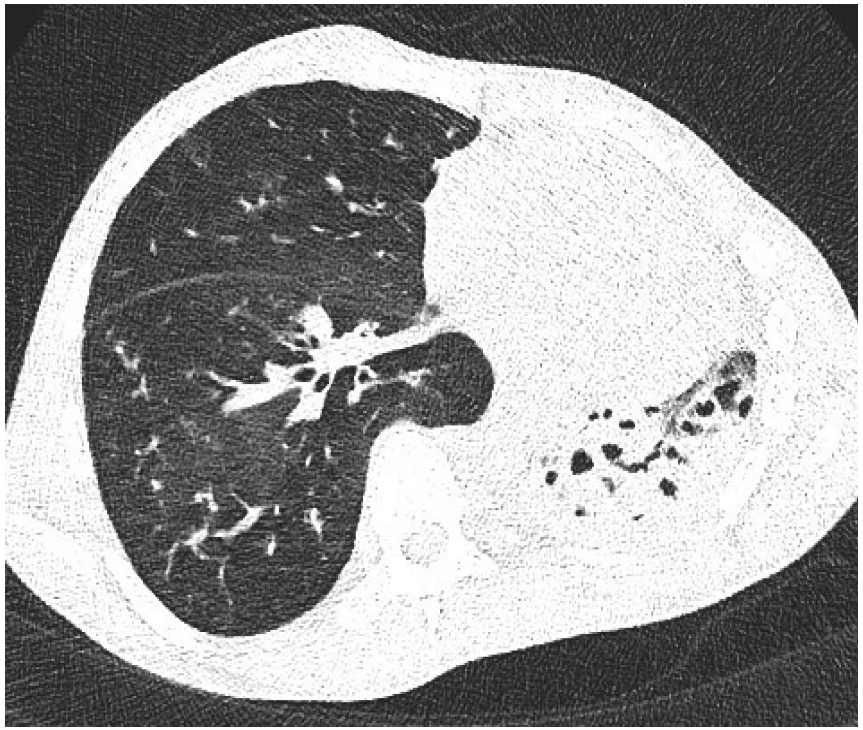
Importance

- If left untreated, CSLD
  - impairs general health
  - reduces quality of life
  - reduces life expectancy

*Kapur et al 2012 & Steinfort et al 2008

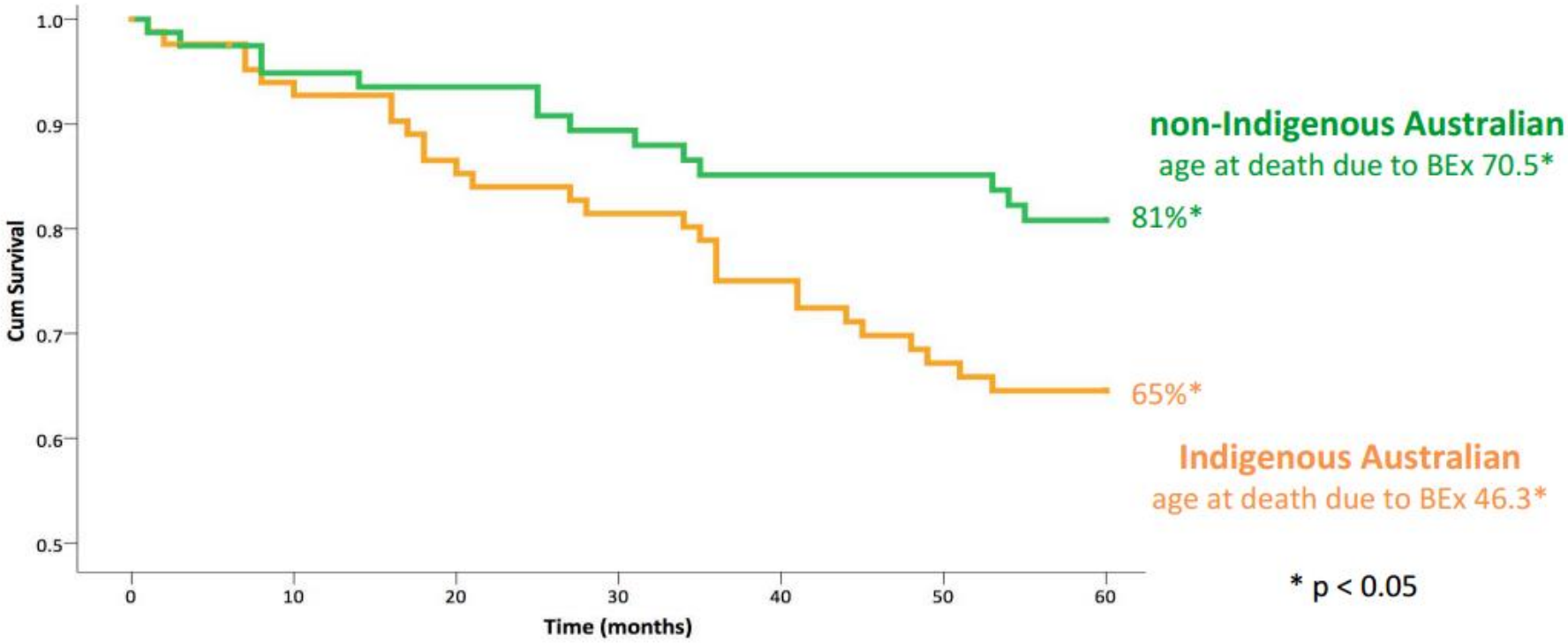
Same adolescent patient, 3 years between CT scans with no treatment





Survival

Figure 1. Five Year Respiratory Related Survival



Blackall et. al. 2015

What tools do we have? National Guidelines

POSITION STATEMENT

Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand

A position statement from the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation

TSANZ The Thoracic Society of Australia & New Zealand Inc

Anne B Chang, Scott C Bell, Cass A Byrnes, Keith Grimwood, Peter W Holmes, Paul T King, John Kolbe, Louis I Landau, Graeme P Maguire, Malcolm I McDonald, David W Reid, Francis C Thien and Paul J Torzillo

The Australian Lung Foundation "When you can't breathe....nothing else matters"™

Although regarded in high-income countries as an orphan disease,[1,2] bronchiectasis remains a major contributor to chronic respiratory morbidity in less-affluent populations, both Indigenous[3] and non-Indigenous.[1,4,5] Moreover, delays in diagnosis of bronchiectasis of years to decades commonly occur in children[4] and adults,[6] and it is likely that many remain undiagnosed and untreated, risking premature and accelerated pulmonary decline.[7,8] This position statement from the Thoracic Society of Australia and New Zealand (TSANZ) and the Australian Lung Foundation (ALF), developed at a multidisciplinary workshop, presents consensus recommendations for managing chronic suppurative lung disease (CSLD), including bronchiectasis, in children and adults in settings other than remote and rural Indigenous Australian communities; recommendations for these communities are available elsewhere.[3] This statement provides an overview and is not intended to replace individualised specialist care. As with all guidelines, it does not substitute for sound clinical judgement, particularly when addressing such a phenotypically heterogeneous condition as bronchiectasis.[9] The development process undertaken by the working group is outlined in Box 1 and the full position statement will be available on the TSANZ website (http://www.thoracic.org.au/).

ABSTRACT

- Consensus recommendations for managing chronic suppurative lung disease (CSLD) and bronchiectasis, based on systematic reviews, were developed for Australian and New Zealand children and adults during a multidisciplinary workshop.
- The diagnosis of bronchiectasis requires a high-resolution computed tomography scan of the chest. People with symptoms of bronchiectasis, but non-diagnostic scans, have CSLD, which may progress to radiological bronchiectasis.
- CSLD/bronchiectasis is suspected when chronic wet cough persists beyond 8 weeks. Initial assessment requires specialist expertise. Specialist referral is also required for children who have either two or more episodes of chronic (> 4 weeks) wet cough per year that respond to antibiotics, or chest radiographic abnormalities persisting for at least 6 weeks after appropriate therapy.
- Intensive treatment seeks to improve symptom control, reduce frequency of acute pulmonary exacerbations, preserve lung function, and maintain a good quality of life.
- Antibiotic selection for acute infective episodes is based on results of lower airway culture, local antibiotic susceptibility patterns, clinical severity and patient tolerance. Patients whose condition

Measuring prevalence of chronic moist cough?

Methods:

1. Physiotherapist with training in paediatric respiratory medicine will visit communities at set time intervals to measure the prevalence and persistence of moist cough in children. Demographic and other relevant information will be collected simultaneously.

Three visits each a month apart to 4 communities

Improving recognition and management of chronic moist cough

Methods

1. Qualitative research investigating enablers & barriers for a) families and b) Health Practitioners
2. Develop 2 interventions
   a) education program for families on earlier recognition of moist cough
   b) up-skilling of health practitioners for earlier detection & treatment of chronic cough and CSLD
4. Implement intervention
5. Measure effectiveness of interventions through pre and post intervention measures.

Where are we at so far?

- Cough Prevalence Study: community engagement to decide which 4 communities to conduct the study followed by ethics submissions.
- Improving recognition and management of chronic moist cough study: WAAHEC, UWA and KAHPF approval
- Next week commencing chart review process and structure of qualitative assessments
- Following chart audit, commence qualitative interviews with families and primary health practitioners

Respiratory health theme: knowledge gaps and future goals

- Surveillance:

  Complete aetiology studies and transition these studies to focus on:
  - Understanding transmission dynamics and seasonality of prevalent patterns
  - Optimising traditional diagnostics and explore new technologies using stored samples
  - Examining the pathogenesis of and predictors for severe respiratory disease
- Management and Prevention:

  Use existing data and the collaboration to initiate further clinical trials
  - New vaccines and/or Optimised vaccination schedules
  - Antimicrobial interventions to prevent chronic lung disease
- Policy and Practice:

  Develop more appropriate management and prevention strategies for Aboriginal Australians and those residing in Tropical areas
  - Modify diagnostic and empiric treatment strategies
  - Vaccination schedules
  - Multi-modal interventions studies for high risk populations

Thank you for listening…